National Heart, Lung, and Blood Institute

Report on Public Responses

Public Health Applications of Genetic Research in Heart, Lung, Blood, and Sleep Disorders

Responses

Through September 30, 2002

Public Health Applications of Genetic Research in Heart, Lung, Blood, and Sleep Disorders

Information Requested

1. Please comment on the optimal balance between a public health approach (population-based or population subgroups) vs. a clinical (patient-based) approach to applying genetic research to improve health and prevent disease. Comments on the appropriate timing and coordination of patient-oriented and population-oriented efforts are also sought.

2. Please suggest additional infrastructure, statistical methods, technologies, consent procedures, population resources, data sharing policies, etc. for enhancing public health applicability of NHLBI-supported genetic research.

3. Consider and recommend approaches to applying genetic findings from rare monogenic forms of heart, lung, blood, and sleep disorders, such as long-QT syndrome or alpha-1-antitrypsin deficiency, to more common conditions such as arrhythmic death in coronary disease or chronic obstructive pulmonary disease.

4. Please suggest approaches for using genetic information to enhance the effectiveness of preventive and therapeutic interventions by tailoring them to patients or population subgroups. Similarly, consider approaches for using genetic information to reduce the frequency of adverse drug reactions and suggest strategies for implementing these approaches.

5. The possibility that an individual's knowledge of their own high-risk genotype could improve their adherence to interventions is intriguing, but has yet to be investigated. Please consider the potential importance of this area and suggest approaches to determining the impact of genotypic information on adherence to interventions by an individual or their family members.

6. Please recommend strategies for using genetic information to identify patient or population subgroups at high risk of heart, lung, blood, and sleep disorders, including criteria that might be used to determine which genetic variants to screen for, and in which subgroups. Please suggest how additional information needed to determine such criteria could be obtained. Suggestions are also needed on which screening approaches to use and when (such as population-wide vs. targeted or high-risk groups), and what information to provide after screening.

7. Please suggest approaches for utilizing NHLBI's large body of population-based observational studies and clinical trials to enhance public health applications of genetic information, including barriers encountered or anticipated and approaches for dealing with them. Brief descriptions of these studies are available at http://apps.nhlbi.nih.gov/popstudies/.

8. Please recommend priorities and approaches for whether and how NHLBI might improve the understanding and utilization of genetic information by the general public (including specific population sub-groups as necessary) and by practicing clinicians.

9. Other information not specifically addressed by the comments above, but considered important and relevant to the use of genetic information in heart, lung, blood, and sleep public health efforts, would also be of considerable interest and value.

RESPONSE 1: BALANCE

Please comment on the optimal balance between a public health approach (population-based or population subgroups) vs. a clinical (patient-based) approach to applying genetic research to improve health and prevent disease. Comments on the appropriate timing and coordination of patient-oriented and population-oriented efforts are also sought.

Both patient-oriented and population approaches are needed—and probably in equal measure. We have a very limited understanding of the role genomic variation plays in disease expression in general, and in certain environmental contexts in particular. Much work is needed in the clinical arena for understanding how genetic variation/mutations contribute to clinical disease, and also how treatments can be (a) targeted to specific subgroups, and/or (b) new treatments created based on newly discovered genetic pathways.

Clearly, both population-based and clinical approaches are needed to understand and reduce genetic susceptibility to disease, especially for complex, multifactorial diseases. In contrast to the long-standing medical genetics emphasis on patients and their families, the emerging field of public health genetics (PHG) focuses on populations and communities, and the potential for "phenotypic prevention" of disease in these groups. That is, we need to better understand gene-environment interactions that could lead to effective behavioral and/or environmental interventions on a large scale. It is also critical that PHG examines the ethical, legal, social, and economic implications of applying genetic knowledge to improve health in populations.

Thus PHG is a multidisciplinary field, involving collaborations between a variety of health professionals. In addition to the traditional public health disciplines (epidemiology, biostatistics, environmental health sciences, pathobiology and health services) and human geneticists and molecular biologists, applying genetic knowledge to improve public health needs to involve social scientists (including cultural anthropologists, bioethicists, and behavioral scientists), legal and policy experts, as well as a variety of other health professionals, (including nutritionists, nurses, pharmacologists), and experts in health education. To be successful, PHG needs to develop new paradigms for effective interactions between these diverse disciplines.

Based on findings from multidisciplinary population-based studies of candidate genes and gene-environment interactions, clinical trials can then be developed to specifically test the effectiveness of environmental and behavioral interventions, including studies that stratify by genotype. Recent experiences from the CARET Study and WHI illustrate that the findings from observational studies must be rigorously tested, and this applies to genomic studies as well. If an intervention is found to be effective in a specific genotype group, it may then be possible to come full circle and apply that on a population basis.

The Secretary of Health and Human Services Donna Shalala chartered the Secretary's Advisory Committee on Genetic Testing (SACGT) in June 1998 in response to recommendations of two working groups commissioned jointly by the National Institutes of Health (NIH) and the Department of Energy (DOE) for the Human Genome Project.

I would like to comment on a subset (in my opinion, an important one) of this particular issue.

My background is that of a practicing family physician (currently 23 years) with a lifelong interest in genetics. I have been fortunate enough to also have been involved in many aspects of

genetics ranging from contributing to peer-reviewed literature on the genetics of dysmorphology, conducting field research in genetics, providing individual genetic counseling services at a university training program, personally performing DNA diagnostic lab work in an accredited clinical lab, and most recently involved with a large epidemiologic/genetic linkage study of cardiovascular disease among American Indian communities. This has allowed me to view genetics from the perspective of researcher, primary care provider for an ethnic minority, genetic counselor, laboratory worker, and finally as the parent of a child involved with genetic research (naturally not my own research efforts!).

The specific issue that I would like to comment on involves the interpretation that results of individual genetic testing can never be revealed to individuals unless developed in CLIA certified laboratories.

The context of this issue arises in a research project that I am currently involved with, studying possible genetic linkage of cardiovascular disease and risk factors. The laboratory that is to conduct the testing is a non-profit, highly qualified lab, with extensive experience in genetic testing. This lab is currently not CLIA certified; and has little incentive to obtain this certification, since there are no plans to provide results to research participants, or to ever conduct testing on a clinical, or fee-for-service basis.

In our consent forms we have emphasized to potential participants the fact that this research is designed to answer epidemiologic questions about populations, and that since we are searching for linkage, there is extremely little chance that specific disease mutations will be found that could be used to provide clinically useful, individualized genetic advice regarding cardiovascular disease or risk. Even if a functional gene was discovered during the course of this research, it is (again) highly unlikely that specific disease/risk causing mutations would be discovered and correlated sufficiently with disease phenotypes, to be confident the clinical utility, and validity was sufficient to warrant recontacting participants and attempting to provide genetic counseling about their individual findings. Our consent forms also outline the general problem of CLIA certification (both for our research group and the participants) and the fact that our laboratory is not currently CLIA certified. The study will probably be funded for a 5 year period; but prior phases have been funded for the preceding 12 years and subsequent phases are likely to be funded beyond the coming 5 years.

In spite of the above, the possibility exists that some information is developed about a gene and various mutations or polymorphisms that could allow individual counseling about increased or decreased risk of cardiovascular disease; or possibly even conditions that were easily amenable to directed dietary or other intervention. These genetic changes could also be discovered by researchers in other studies; and reconfirmed by results from our program. This would allow greatly increased confidence in the validity and applicability of this finding. Should this occur, our research group would feel an obligation to share this information with our participants (and indeed we commit ourselves to such action in our informed consent); but will be in a very difficult situation regarding the CLIA regulations.

After discussion of this with officials at the CDC/CLIA office, ethicists and other researchers, we feel our options are limited to:

1. Revise our consent to inform participants that they will NEVER receive individual genetic results from our program, no matter what is discovered or when, since we can not provide CLIA approved results.

2. Leave our consent as it currently stands, and attempt to obtain CLIA certification in the event a clinically significant discovery is found. (The advice we have received about the feasibility of this, and whether all of the lab testing would have to be redone, is inconsistent).

3. Leave our consent as it currently stands, and refer participants to CLIA certified labs for retesting if a clinically significant discovery is found.

Each of these options have their advantages and disadvantages.

Participants will NEVER receive results.

Advantages: Very narrowly defines our responsibilities, participants should have essentially NO expectations of personal gain.

Disadvantages: Participants truly have NO possibility of individual benefit, even though some is potentially available. Regardless of consent agreed to, participants may seek individual information via legal, political, or regulatory (e.g., Freedom of Information Act) means, if they become convinced that individually useful information is available. We highly doubt the political will to resist these requests, if they come to pass.

Obtain CLIA certification IF a clinically significant discovery is made.

Advantages: Relieves the lab of the expense and effort necessary to obtain certification, which is almost certainly never going to be of benefit to the lab.

Disadvantages: We have no solid information to indicate that this option would be allowed (in other words we might be forced to start again from scratch, after certification was obtained, redrawing samples, rerunning analyses that had already been completed). The availability of funding to do this is also unknown, as grant funding for the original project could well be completed.

1. Refer participants to CLIA certified labs IF a clinically significant discovery is made.

Advantages: Our lab avoids the cost and effort of obtaining certification. Participants obtain the ostensibly more accurate results of a CLIA certified lab.

Disadvantages: The chances are very great that there will be no CLIA certified lab available that can do these tests. In the early stages of such a discovery, there will be considerable uncertainty about the economic feasibility of providing such tests. A

commercial/CLIA certified lab will have to consider their investment in developing the test procedure, liability exposure, potential losses from other more lucrative projects that will be delayed etc. There are currently many known genetic diseases with cloned genes and defined mutations that have gone years with no apparent interest by CLIA approved labs in providing service for the condition.

Secondly, the question of WHO will pay for this service by a CLIA approved lab, outside of our research group? It will be the height of irony that participants will know that their individual results are denied to them, and that they must wait until a CLIA approved, most likely commercial lab, develops this test, retests them and then charges them for results that they helped to develop! This irony will not be lost on their legal representatives, their public relations counselors, or their state and federal legislative representatives (in spite of the fact that it was these same representatives that created this legal/regulatory framework).

While I have outlined the crux of the problem our research group faces; this is actually a more extensive problem. I alluded to the fact that there are currently genetic diseases with no apparent interest by CLIA approved labs in providing service for the condition. These are by no means trivial, "cosmetic" conditions with no means of amelioration. The Long QT syndrome due to mutations in the KVLQT1 gene (and others) causing cardiac arrhythmias and sudden death, often in children, is a good example. This gene was cloned and characterized in 1996, but today there are still no CLIA certified US labs that provide testing for this condition. There is one US lab that provides the test on a "research" basis (thus ostensibly precluding patients or participants in this research project from obtaining their individual results for this frequently fatal condition). I know from personal observation and discussion with others in the genetic community that in many instances results from testing done in research labs such as this do indeed find their way to the participants involved; but the legal and regulatory pressures of CLIA have made this much less common. Many labs have removed themselves from GeneTest (previously HELIX) listing for fear that their results were being transmitted to patients and they might be held responsible.

Just imagine for a moment that you are a researcher or clinician explaining a research program on Long QT syndrome to parents of a child that may be at risk. You would like them to participate in the testing, they would like to know if their child has a mutation in this gene (that they may have seen cause the death of a couple of other children in their extended family); but you have to explain that you will NOT be able to give them the results of their child's test because there is no CLIA certified lab available to do this test.....and by the way, if they agree to participate....you would appreciate them notifying you if their child dies suddenly because that will help to clarify the genotype/phenotype relationship this research group is interested in? How would it be possible to face a family with this scenario?

What I have been trying to point out is that a law that was designed to prevent abuses of commercial, shoddy, "sweat-shop" cervical cytology services has been interpreted as also regulating the provision of important individual information to participants of research efforts. In addition, the law has had and will have a very inhibitory effect on the provision of testing services for rare diseases that will never have the economic interest of conditions such as hereditary breast cancer and others which are currently demanding so much attention.

I recognize the abuses and commercialization of many areas of medicine. I strongly sympathize with the need for regulation of many aspects of medical care; but I am also aware that the regulation of anything entails expense that will inevitably be paid by someone. Simply establishing stringent requirements for quality and consistency and then allowing market forces establish the provision of services is NOT a plan that will produce a rational and equitable system in all situations. My prediction is that we will be hearing more complaints about "orphan" genetic tests (analogous to "orphan" drugs) in the near future. This balance between ensuring quality services and the negative effect on availability due to increased cost was mentioned on numerous occasions in public comments regarding CLIA in the Federal Register of 2/28/92. A number of pleas to exclude research laboratories was also rather summarily dismissed. I believe CDC has overstepped it's mandate in this interpretation of CLIA. The fact is that the establishing legislation for CLIA stipulates that the regulation is to pertain to testing "for the purpose of providing information for the diagnosis, prevention, treatment of any disease....". I believe the operative word here is "purpose". Most clinical laboratory work is done for the "purpose" of providing clinical care. The "purpose" of medical research is primarily to answer scientific questions about disease. There are times when lab testing is needed in the course of medical research to guide therapy etc; and I think the requirement for CLIA certification is justified in that instance. On the other hand, when information is developed during the course of research (as a side product so to speak), and could be useful to the individual participant; then it should be available to them.

In my opinion, the primary means of distinguishing this situation is the matter of compensation. If the testing is being conducted without payment by the participant or through some insurance mechanism; then CLIA regulations should not apply. The only qualifiers to this would be in the case of testing necessary to guide the clinical provision of care in some studies (as mentioned above) and to ensure that informed consent of the research participant explained the non-CLIA status of the lab results.

As may be expected from the preceding arguments, I DO NOT feel that genetic testing requires additional regulation beyond that provided for under CLIA. I do feel that genetic testing should be considered a specialty (analogous to cytogenetics, immunology etc) under CLIA regulation. I strongly feel that testing conducted in a research mode, without compensation to the laboratory (from the participants or their agents), should NOT be regulated under CLIA.

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1. Population based vs. patient based approach:

In the case of population based studies, screening tools need to be developed, e.g. for gene expression studies, methods are needed to develop a fingerprint of gene expression changes that are predictive of likelihood of development of disease risk in a particular individual. Ideally, the gene expression fingerprint should be specific enough to predict not just heart failure in asymptomatic people, but ideally it should even be predictive a specific heart failure etiology. This type of approach has successfully developed for gene array screening of cancer subtypes (e.g., Bhattacharjee et al., PNAS 2001, 98:13790–5,). However cardiovascular disease presents its own unique challenges.

If we continue to use heart failure as an example, the question we need to address is: what is the best way to screen for an individual's predisposition to develop ischemic or dilated cardiomyopathy? To date, SNP analysis in sib pairs has generally been disappointing (e.g., Gura et al., Science 2001, 293:593–595) and no new genetic mutations have been unequivocally linked to predisposition to develop dilated cardiomyopathy. To our advantage is that fact that we now have most of the methods in hand to allow us to obtain a fingerprint of gene expression changes that could in the future, predict disease development. These include laser microdissection to obtain RNA from cell types of interest from complex tissue samples and amplification of RNA from very small samples. In distinct contrast to the ready availability of tissue for phenotyping of tumors, cardiac biopsies from asymptomatic people are not feasible for screening purposes, because of the inherent risk associated with this invasive procedure. Thus unless this situation changes in the future, we will need to consider alternative approaches (please see response to item #6 for a proposal).

The patient-based approach:

As discussed above, it is rarely possible to obtain biopsy samples from asymptomatic people in the general population. However, since cardiovascular disease is obviously already present in patients, tissue samples (e.g., explanted failing heart, tissue removed during LVAD insertion or removal of septum in patients with hypertrophic cardiomyopathy) are much more readily available.

In gene profiling studies, as well as proteomic studies, on human myocardium from heart failure patients, we can ask quite a different question than we would ask in population based studies: what are the underlying mechanisms that trigger development of disease, and how can they be distinguished from secondary or compensatory changes that occur with disease progression?

The goldmine that we are searching for is changes in expression of a gene or gene product, or altered function of a protein, as a result of a mutation, in the context of a metabolic or signaling pathway which, when targeted by therapeutic intervention, will result in reversal—or ideally—prevention of disease development.

Some potential and promising ways that this can be achieved is:

Extension of gene array studies to the next step: to understand gene expression changes in the broader context of altered signaling pathways, e.g., by programs such as GenMAPP (http://www.genmapp.org/introduction.asp)—gene expression changes can be superimposed upon known signaling pathways to help identify consistent changes in gene expression. Potential changes in signaling or metabolic pathways can then be explored in transgenic mice or by gene transfer to rodent hearts in vivo.

1. Animal models of heart disease are, in theory, a valuable adjunct to direct measurements of gene expression changes in human tissue. However to date, both correlation of disease-specific (as opposed to animal model specific) changes across models of cardiovascular disease, as well as correlation of changes across gene and protein array platforms, is still in its infancy. Lack of progress in this field results in

large part from a general failure to integrate information obtained across animal models as well as across gene array and proteomic platforms. Before we can take the results of these studies back to the patient, more work will still need to be performed to identify both changes in gene and protein expression, changes in protein-protein interaction and even altered post-translational modifications that are common to a particular disease, as well as changes that are unique to a specific etiology (see for example Tan F., et al., PNAS 2002, 99:11387–11392. Furthermore, a major advantage that animal models can offer which could complement microarray studies of diseased vs. non-diseased human myocardium, has not yet been fully exploited—namely, identification of changes in gene expression as a function of disease development and, where possible, disease regression. All of this work could be greatly facilitated by availability of a publicly funded multi-institutional data base—perhaps something similar in conception to one of the NIGMS Glue grants (e.g., the NIGMS sponsored Alliance for Cell Signaling http://www.nigms.nih.gov/news/releases/gluegrant_release.html)

The UK (where the respondents work) has adopted a two-fold strategy towards post-genome research. First, existing population-based studies such as the Whitehall II study and the national Birth Cohorts (e.g. 1946 and 1958 Cohorts) have collected, or have received funds to collect, DNA for studies involving common SNPs in relation to cardiovascular disease (CVD)and respiratory disease. Second, the new UK biobank will be patient-based. There are advantages and disadvantages to each approach, however the need for replication, and to search for important differences in effect size (whether gene, gene-environment or gene-gene effect) means that population and patient oriented research must proceed side-by-side in order to reduce errors in this rapidly developing field.

Another example comes from comparison of results from twin studies, which tend to emphasize the importance of inheritance for conditions such as obesity, as opposed to those from cohort studies which provide strong evidence for the importance of childhood environment.

A quick response to your request to a nongeneticist for advice on genetics.

Off the cuff:

Access to large populations with high quality information on phenotypes will be important. Establishing a common searchable electronic medical database linked to banked DNA samples for all patients enrolled in NIH-sponsored trials might be useful. This might be set up with input from large medical centers or groups of them (?University of California system) or HMOs (Kaiser) so that the system could be adopted more widely.

Deep resequencing of candidate genes in patient populations seems likely to yield useful clinical information (but perhaps not novel biology). Candidates include:

Genes known to cause diseases with mendelian inheritance. Look for SNPs that cause smaller (but still important) effects. LQT genes are examples.

1. Genes selected from pathways known to be involved in cardiovascular disease. Identify "rare" SNPs that have large biological effects. Genes involved in lipid metabolism (recent 7alpha hydroxylase story) are obvious examples.

What seems to be the goal of many that have pushed a genetic approach to understanding CAD risk is a set of useful markers of disease risk that might be used much like risk factors to predict risk at an individual level. With the advent of sufficiently high resolution, non-invasive visualization of the coronary arteries, it may be less important to measure risk factors (we will be able to "see" the disease, not just predict it). Nevertheless, some would argue that knowing whether an individual was at high risk due to genetic make up might allow a particularly aggressive, targeted approach to preventive efforts. This approach, almost by definition, is patient-oriented. The potential utility of this approach is in no way conflicting with the importance of population-oriented efforts to reduce risk.

In order to have a useful "panel" of coronary risk-related genes, we must show consistent ability to predict risk with all the genes in the panel (or some other clear utility). The utility, again, of such a panel would be to identify persons at higher risk and focus on more vigorous standard risk factor intervention.

Another possible utility at identifying new genetic risk markers would be to help find potentially useful novel interventions and further insights into the disease process. There may be utility, also, for identifying genes that predict response to medications (especially for HTN intervention).

Presumably, the optimal balance that is sought is on the financial balance sheet: research expenditures versus patient care. In a perfect world the balance would be fifty-fifty with the timing and coordination of patient-oriented and population-oriented efforts coincident. For example, in the case of obesity, a 50% budget expenditure on gene discovery, epistasis, gene-environment interaction, and examination of possible behavioral intervention with the remaining 50% on education or exposure of the public to validated behavioral interventions.

First, let me disclose a submitted NHLBI grant on this issue.

In the sleep disorders, the most obvious area for genetic exploitation is the circadian rhythm sleep disorders, which are known to have a strong genetic basis. The heritability of the morningness-eveningness scale is about 0.5. These problems are more common than has been recognized. Since most of the circadian clock genes have probably been identified, it is now a straight-forward problem to determine the genetic variants in circadian clock genes and see how they are linked to the circadian rhythm sleep disorders.

A second issue is sleep length, which appears from twin studies to have a large genetic component. Classic linkage methods, e.g. in sib pairs, could find the genes determining sleep length, if there are a relatively small number of large-effect genes.

I think an equal balance is best. Population based studies may be good for discovery, but patient based studies can help determine mechanisms.

It is a pleasure to have an opportunity to respond to the questions that you have posed. Again, NHLBI is in the forefront in recognizing the broad public health issues raised by basic science research.

Before commenting on the specific questions, I will share two background concepts. The first regards the unique status of genetic research in the minds of the public and elected officials. In order to justify the billions of dollars invested in genetic research, the public has been told that cures for common diseases are near at hand. We will create perfect children and cure the diseases of aging by genetic manipulation. Those in the field are well aware that such advances are far in the future and many basic scientists see the understanding of mechanisms as much more important than any practical applications. The field has been hyped and public expectations far exceed progress to date. Throwing more money at basic science research may not solve this problem just as it failed in confronting the HIV epidemic. Twenty years later we are closer but do not have a solution to HIV/AIDS despite investment of billions of public dollars. However, assuming that genetic advances do result in practical health applications, this is the time to begin thinking how that might occur.

The second thought relates to the entrepreneurial economics pervasive in genetic research. Michael Crichton (HMS ‘68) describes this in his book, “The Lost World: Jurassic Park.” As he describes the scientific revolutions of the 20th century, he compares the genetic revolution with the discovery of nuclear fission. In the nuclear fission example, a few brilliant physicists revolutionized thinking on how matter and energy interact at the subparticle level. None of these scientists expected to nor did they benefit economically from their extraordinary discoveries. Crichton goes on to comment that the genetic revolution is the first time where many scientists, including private, university and government scientists in combination of venture capitalists see extraordinary potential monetary gain from their work. Many well known geneticists have moved from university-based research to proprietary commercial research with the expectation and realization of financial gain. This has changed the dynamics of genetic research and resulted in driving forces which may not be the best for the health of the public. A local example of this came up to two weeks ago in our NHLBI sponsored project on sudden death. Our genetics colleague, Richard King, was interested in a certain gene segment and found that Celera (owned) it and would sell the information to us for $150,000. Such an attitude pervades the genetics field and may result in research directed toward profitability rather than health needs.

Answer to specific questions:

A balanced approach involving both patient and population-based strategies is necessary. It seems to me that given the nature and development of the field, initial efforts need to be focused on clinical approaches where short-term benefits are more likely while not neglecting long-term population-based plans.

As discussed below I think there is enough information presently at hand to begin to apply genetic information for patient-oriented diagnosis and treatment as well as research. An example would be directing patient care based on phenotype-genotype correlations for various genetic forms of sudden cardiac death in which knowledge of the genotype already provides important clinical information that can be used to direct therapy and provide prognosis. In more complex multi-gene diseases population based approaches are warranted including studies designed to identify high and low risk subgroups as well as pharmacogenomics (responders, non-responders and adverse responders) using genomics and genetics.

The two approaches are complimentary. Population-based approaches are expensive in the sense that any given adverse event is rare, so large samples are required. However, for common diseases, the population approach is a good idea. Further, the allele frequencies of polymorphisms must be determined in virtually every ethnic and racial group separately, which could benefit from population subgroup approaches.

However, especially for the hundreds of rare disorders, disease based (better, family based) approaches are absolutely critical, and funds must remain available.

From a public health perspective, one critical issue is that proprietary angles on DNA samples from rare populations or rare disorders, must be discouraged, in favor of sharing.

One important way to decrease the inequities in health care, is to emphasize more public health measures that also saves on health care dollars.

I have been able to make advances in the potential field of gene therapy for hypertension and cardiovascular disease, because of the flexibility of the award to pursue new ideas and the stability of funding which allows me to retain some devoted, highly competent staff. However as a basic scientist I have also experienced the BIG GAP of moving the results of animal experiments to human studies. There is no BRIDGE to get there. To move from the lab to even a phase one trial seems out of reach. I have given several key note talks at conferences of physicians and the most frequently asked question is “when will that be available for us to use?”

It is a question I can not answer. It seems the only possibilities are

A big pharma company swoops in takes over. However after talking to Merk and other big pharma companies they are reluctant to enter gene therapy for cardiovascular disease such as hypertension.

1. A small venture cap company which can be formed around the ideas and involve the investigator. This is fraught with conflicts of interest.

At first we did not even think of patenting so some potential products are not patented. This reduces the potential offering of products to a venture cap company. We felt forced to patent recent products such as antisense to beta 1 adrenergic receptors, antisense to angiotensin converting enzyme and vigilant vectors for the prevention of heart damage during ischemia. Frankly I am not interested in business, but I do believe that so much NIH supported research comes to nothing because of this gap and lack of a bridge to patient care. So here is my suggestion: Create a program to provide the bridge over the gap. Involve business, clinicians and patient representatives to review basic science ideas that have great potential for better treatment or cures. Let the study sections approval rating be publicized as a way of encouraging business to support the future development of the ideas into clinical practice.

I remain skeptical that genetics will do much to improve public health for any disease category although the question is an empiric one and requires further study. Clinical studies are likely to be fruitful in limited settings, and there are examples in monogenic disorder with gene transfer in hemophilia and severe combined immunodeficiency. The other type of successful examples comes from cancer--for instance, the development of the tyrosine kinase inhibitor for CML. I am envious of the folks who work in cancer. Their model is so much more elegantly simple. For that reason, I remain skeptical that gene transfer or similar clinical studies will be fruitful lines of research in cardiovascular disease. We are still early in the research process, and the several lines of research remain important until we know more.

I am pleased to respond to your recent Request for Information about future public health applications of genetic research. Our laboratory has been engaged in genetic studies of autoimmune disease, including inflammatory heart disease, for a number of years. We believe these studies will find application in public health in the following areas:

1. Prevention and Prognosis

In 1971, we were able to show that we could predict the susceptibility of a mouse to an autoimmune disease, thyroiditis, based on its H-2 haplotype. This was the first time a particular genetic trait was associated with an autoimmune disease. Soon afterwards, we were able to predict the likelihood of spontaneous thyroiditis in OS chickens, based on the B blood group, the avian MHC. Since that time, many efforts have been made to utilize the human MHC to predict susceptibility to autoimmune disease with relatively little success. The problem is that the genetics of inheritance in humans is quite complex and more information is needed about other, non-MHC, genes that contribute to susceptibility. We are presently unraveling such genes, using an experimental model of autoimmune myocarditis in mice and have already found preliminary evidence that several of these non-MHC genes are shared with other autoimmune disorders, such as lupus and Type 1 diabetes. To actually demonstrate that the same gene is involved, however, will require extensive refinement of localization and eventual development of congenic mice. The next step would be to identify human homologues, requiring a combined effort with many

laboratories and institutions. Developing cooperative groups to pursue the goals will permit us eventually to identify individuals within families, and even within the general population, who are sufficiently at risk of developing an autoimmune disorder that careful surveillance and even preventive interventions would be justified. The goal of this approach is to prevent rather than reverse an on-going, destructive autoimmune process.

2. Future Therapies

The most significant bottleneck in translating genetic research in human diseases to therapies is not in the identification of genes, although this is a significant challenge, but in understanding the function of genes. Functional analysis is most efficiently performed in animal models. Therefore, investments should be made in:

a. identifying animal models of human disease, especially small rodent models. These models will not only be important in functional analysis, but also in the trial of proposed therapies.

b. bringing the non-human genome projects up to speed, especially the mouse genome project.

c. development of mouse and human genomic DNA contiguous libraries in YAC and BAC constructs.

d. expansion of cDNA and EST libraries, and increase of availability to the whole research community.

e. development of centers which can assist or efficiently perform genetic engineering in animal models (i.e., transgenics, knock-outs, knock-ins, etc.).

Some methodologic research is required to answer this question. We don't know with certainty the number of genes involved in the specific diseases of interest to NHLBI, the penetrance of these genes (relationship between genotype and phenotype), and the relationship between genes and diseases. One approach would be to design a database to be able to address specific effect sizes with a specific degree of certainty. Negative studies in this database would really represent the upper confidence interval of an effect size. Further investigations for relationships would require datasets with a greater ability to answer questions about smaller effect sizes. This type of logic can be applied to clinical and population-based data sets. Obviously, clinical data sets may be more efficient for detecting relationships between genes and disease, while population datasets may be best structured to address prevalence questions.

Rationale: It will be far quicker (and therefore more cost effective) to determine relevant genetic variants that influence cardiovascular outcomes in clinical (patient-based) trials since studying large populations over time takes decades. Note that such trials are not necessarily classical therapeutic (clinical) trials, but rather genetic association studies between markers and disease endpoints. The information gleaned from these trials can then be taken back to larger population studies. Using current large population databases, even if genetic data were available, does not give rigorous enough clinical endpoints to be used effectively at present either.

Here are some thoughts regarding the solicitation for input on applying the results of genetic research:

In general, I would support a balance of public health and clinical approaches to applying genetic research. The emphasis should reflect the goals being addressed. If the goal is to enhance risk factor stratification in the general population, a population-based approach is appropriate. If the goal is to use genetic data to tailor drug therapy for hypertension, for example, a clinic based approach might be more useful. The issue of timing and coordination are likely to be important; and, the specific approach will again depend on the goals. I suspect that in some cases population-based work should proceed clinic-based, while in other cases, the order might be reversed.

Both required, and both require a science based approach.

Initial studies and pilot studies might be patient-based and followed by studies of patient subgroups and defined populations.

It is difficult to separate population-based approaches from clinical (patient-based) approaches in genetic research. Careful and through analysis of patients may shed clues that need to be verified or validated in family studies. The dissection of the genetic clues then often involves studies of larger population sub-groups.

It seems that both are needed, but that there needs to be much more emphasis in improving our underlying understanding of the basic biology and biochemistry of the effects resulting from the genetic disorders.

Clinical genetics, in those cases in which we really know a genetic risk factor, can be effective. In addition, when we really do know a genetic risk factor, highest priority should be given to seeing whether that genetic knowledge can actually be put to direct use beyond genetic counseling. I would say this should get higher priority than ever more costly mapping searches to find new candidate genes.

Population association studies have well-known problems and I think this type of research should be greatly de-emphasized until we figure out how to do it so it generates believable, usable, replicable results. The same is true of genetic and of environmental epidemiological approaches.

Technology matters most and works best when applied to a problem for which it is suitable. This is likely to be most true in genuine genetic disease, where risk is stable, clear, and estimable. Effective application to public health—if we ever figure out how to do it—will be much less dependent on technology as we currently apply it.

Genetics involves the analysis of linkage to a particular phenotype. There are many disorders in which the physician has to make an accurate diagnosis. With such good phenotyping, it is possible to find an associated genotype. This analysis works for many single or strong genes. It must be continued. In conjunction with this, it is possible that SNPs will define disease loci. This also should be investigated. Proof of gene function in this case requires excellent animal models or biochemistry. I would favor a 50-50 split.

RESPONSE 2: INFRASTRUCTURE

Please suggest additional infrastructure, statistical methods, technologies, consent procedures, population resources, data sharing policies, etc., for enhancing public health applicability of NHLBI-supported genetic research.

Creation of easily-accessible, well defined case-control study samples for rapid export of newly detected SNPs/haplotypes/mutations for association studies. For example, create an early MI onset case group with a large number of cases/controls representing the major ethnic groups in the US. The same could be done for ischemic stroke, heart failure, etc. This would serve as a resource/sample repository that could be stored at NIH. We shouldn't continue to recreate new case-control studies every time we want to test a new SNP.

One of the clear problems with family-based genetic studies is the lack of statistical power. NHLBI is funding several family studies that individually may lack sufficient power but if they were pooled might achieve significant results.

A centralized database that pooled the data from all these studies is an excellent idea. In order to insure privacy there would have to be a mechanism to restrict access to qualified investigators, but this is not a major barrier.

Certainly the investigator who gathered the data deserves exclusive access for some period as a reward for the gathering effort. However, data that is not only older, but on which the initial research is complete, (there are many such cases) should be made available to investigators who may have new approaches.

In 2001, NHLBI actually began a data sharing initiative, but I have heard nothing more about it. What happened?

In order for genetic knowledge to be effectively applied, it must be widely accessible to public health professionals. Efforts such a Human Genome Epidemiology (HuGE) reviews in the American Journal of Epidemiology provide one such resource, but more are needed. It is also critical that public health professionals are provided sufficient training to be able to make use of this information. For example, most MPH programs do not require genetics training, leaving these professionals unprepared to make use of the growing body of genomic information. Thus, training of both current and future public health professional would greatly facilitate the effective application of genetics to public health. In addition, genetic researchers would benefit from encouragement to broaden their views from strictly gene discovery efforts to more translational research, for example implementing their finding in high-risk communities

Ethical concerns, including informed consent procedures for such translational research, are often controversial in the context of genetics. For example, the trend for more regulation of research protocols by local IRBs is being applied to community-based research and well as family screening, often discouraging research in these areas. More active collaborative efforts between genetic researchers and bioethicists are needed to insure the success of the research while at the same time appropriately protecting research subjects and their communities.

Once sufficient data is available to support testing for a disease susceptibility gene in public health settings, the appropriate technology must be available to implement to it with rigorous

standards. Currently, at least some genetic research projects do not report genotypes to participants because the test is not CLIA certified in that laboratory, even if the results are clinically meaningful. Obviously, improving technologies for high throughput genotyping in large population groups is necessary for successful implementation of such a screening program. But in addition, policies must be in place to be sure that such testing is equally accessible to appropriate population groups, and that protocols are in place the report genetic test results in culturally sensitive ways.

With the growing availability of SNPs and haplotype data, methods are urgently needed to more fully characterize the linkage disequilibrium (LD) block structure of the human genome, its variation in different ethnic groups, and the implications of these results for case-control genetic association studies. User-friendly methods for haplotyping unrelated study subjects are needed, as is more research on the impact of population stratification of the results of such studies. Most importantly, methods are needed to help identify functional variants with LD blocks of the genome. All of these efforts would facilitate the application of gene discovery efforts in public health.

Because large sample sizes will be needed to understand complex, multigenic diseases, data sharing policies need to be encouraged among investigators. At the same time, such policies must insure that researchers who initiate and obtain funding for data collection activities receive appropriate credit for their contributions when the DNA samples they have collected are then used for genomic studies. To date, the lack of such assurances has often caused epidemiologists to hesitate in sharing data and samples.

As epidemiologists working in population-based research, we are concerned to maintain the support of the general public, which we hope will benefit from our research efforts. It is therefore critical to preserve a balance between the rights of participants, and those of public-health researchers.

The public appear happy to cooperate, as long as there is a view that commercial exploitation is carefully controlled. Our commissioned poll, conducted in 1997, found a dramatic fall in support for genetic research if the results will be used for private profit, without any reciprocation.

The trend towards needing specific consent for specific research objectives could lead us towards an absurd situation in that identification of each of say 250,000 SNPs will require specific consent.

It would be highly informative if there were an accessible listing of current candidate genes and the associated phenotypes that are being investigated as NHLBI supported research projects evolve. Minimal information would include the gene, phenotype, and numbers of individuals being examined. This would provide investigators with the potential for collaborative (data-pooling) analyses, the incentive to enlarge current investigations underway in other cohorts, or to consider abandoning planned analyses.

It may be useful to create a centralized pool of data from all genetic studies in hypertension (e.g. Framingham Study, SCOR's, Family Genetics Studies), including clinical/phenotypic information for each patient and DNA samples. Researchers may submit ideas for use of this resource and peer-review groups may choose which projects have merit to be allowed to use the resource.

There seems to be a problem with the use (more accurately nonuse) of collected genetic samples from NIH sponsored (and other) clinical trials. There appear to be numerous examples where genetic samples were collected and consented for and yet publications do not seem to be streaming from genetic analyses within clinical trials. In some cases it seems that the investigators do not want to do anything with the genetic samples, but they also do not want to share the samples with investigators who do wish to test genetic hypotheses. NIH should insure that for NIH-sponsored clinical trials: 1) genetic samples are routinely collected and appropriately consented for; 2) if the maintainer of the genetics database is not going to do something with the collected genetic samples, that other investigators are not precluded from access to the samples and a mechanism for tying the genetic information to the clinical phenotype information. If there are clinical trials where this is in fact the case, NIH could consider competitive small grant programs where successful applicants would be given access to the genetic samples, and there would be a mechanism in place, with the main trial's data coordinating center, for accomplishing the association analyses. It would seem there is a lot of important genetic information out there that can be tied to huge clinical trials data, and it is a waste to not link the stored genetic samples with the relevant clinical information from the trial.

Data sharing of NHLBI-supported genetic research data ought to be consolidated in a single clearinghouse with the CDC model of NHANES III dataset accessibility as the gold standard.

A multi-center collaboration on human sleep genetics could be valuable. Many sleep clinics characterize patients with circadian rhythm sleep disorders and apparently-hereditary long and short sleep, so a multi-center collaboration might produce a very large and valuable number of well-characterized DNA samples. These could then be analyzed on a collaborative basis.

Translational research is essential for linking genetic mutations with patient mortality and morbidity. To this end, methods that can directly relate genetic and cellular abnormalities with clinical disease are best.

NIH support tends to focus on specific scientific hypotheses and experiments designed to test those questions. Infrastructure support and methodology is less likely to obtain funding as it is more difficult to demonstrate outcomes and will extend well beyond the average four-year grant application. It may be useful to support some "Centers of Excellence" that would have the task of developing methods and providing resources to translate genetic discovery to the health of the public.

There is a critical need for centers capable of high through-put genetic diagnosis of cardiovascular diseases. In addition, there should be centers established by the NHLBI that can provide genetic diagnoses for both research and clinical purposes—relying on individual research labs to set this up is not working. These centers should also provide training for clinicians and physician-scientists in genetic diagnosis and management of genomic information. Partnering with a company also makes sense as there are several genomics companies now that offer platforms for high throughput genetic screening in populations but they lack the access to investigators that the NHLBI has.

Urgent need for intermediate technologies to asses biological impact of information generated by genetic research. New post-genomic technologies, aimed at generating comprehensive protein-protein interaction maps to reveal the functional networks that control cell function, ultimately rely on complementary methods to measure accuracy and relevance of interactions. There is a large and increasing gap between the cataloging of putative causal molecular mechanisms and their actual demonstration. We have been concerned for some time that biomedical hypothesis from static in vitro systems or genetic associations are being translated to animal studies and clinical trials on rather speculative bases. This is particularly obvious for datasets of interactions among proteins involved in surface catalysis, transport and sensing against which high-throughput interaction-detection methods are biased. In vivo, membrane proteins interact with other molecules in the fluid phase to mediate responses within biological transients, that last only seconds to minutes. However, available techniques examine kinetic mechanisms in unrealistic homogeneous solutions or at best, in cell suspensions and under steady state conditions. There is an urgent need to develop flow technologies with live cells or tissues to characterize and mechanistically understand newly proposed genetic connections under biologically relevant conditions.

NHLBI must foster sharing. Grants regarding virtually every disease would benefit from DNA registries, which should be sharable, or be available for collaboration. In rare blood diseases (my specialty), it is distressing to see proprietary groups trying not to share precious resources.

Uniform consents for use of genetic samples would be helpful. The current moving-target strategy for IRBs and genetic consents is not helpful.

Population resources (SNP frequencies in many ethnic populations) would be extremely helpful.

NHLBI-funded repositories or statistical-genetic consultation would be helpful for NHLBI-grantees.

All NIH funded research reagents animal models etc. generated by investigators should be made available to all investigators.

As we move toward the use of multiple SNPs or haplotypes in each gene and examine the associations for sets of genes, the analytic issues have become exceedingly complex and interesting. My reading of the literature is that approaches are being developed and tested (though of course they are not now in statistical packages). The major problem seems to me to be one of multiple testing. If 1 to 3 million associations are tested, how can we sort out the wheat from the chaff? Although there are some useful approaches under consideration (Bayesian, false discovery rates, and so forth), the best defense is replication in other populations.

As you may know, I am representing CHS in the Longevity Consortium, a planning R01 received by Steve Cummings, who has done a terrific job. Over a series of 3 meetings, Steve has brought together the key players from major studies of older adults in the U.S. and Europe, and together we are moving toward a U01-like application that has the best parts of R01 and contract work. Each group proposes a set of candidate genes in a population; where possible, laboratory, statistical, and epidemiologic methods are shared across projects; the governing structure will probably look at lot like CHS or MESA or SOF; both basic scientists and population scientists are involved--this has been great fun; and other cohorts from the consortium provide populations for the rapid validation of findings from any one cohort. I am happy to provide additional details. This brief summary is intended to suggest that the NHLBI might try to encourage a similar sort of “consortium” for CVD. This idea is not new.

I wish to address item related to infrastructure, statistical methods, and technologies. I believe these comments are especially pertinent as I have been an NIH grantee for more than 20 years and also because I have been at a small institution for most of that time. As you can imagine, in such a situation infrastructure is perennially a problem. This problem has become exacerbated by the current rapid rate of advance in genomic technologies.

I would like to address two technologies specifically:

Real-time RT-PCR—an example of this is the system made by Applied Biosystems called the ABI Prism. This technology in my view lies between our standard methods for determining gene expression (e.g., Northern analysis, ribonuclease protection assays, etc.) and more global methods such as microarrays. For example, my colleagues and I have a long-term (again, more than 20 years) interest in regulation of vascular function and angiogenesis. With this technology we are currently evaluating, in the same samples, the levels of mRNA for 15–20 genes related to vascular function and angiogenesis. This is truly powerful technology as it is allowing us to relatively quickly and easily evaluate expression of multiple TARGETED genes of interest and, importantly, I believe, will allow us to model these systems and ultimately to understand their regulation.

1. Fourier Transform Mass Spectrometry—This, in my opinion, is a far more powerful technology than any of those looking at expression of mRNA, including microarrays. This technology allows for identification and quantification of literally hundreds of proteins in complex mixtures including tissue homogenates. I just recently heard a talk about this by one of the developers of the technology, Dr. Donald F. Hunt, Depts. of Chemistry and Pathology, Univ. of Virginia, Charlottesville.

Unfortunately, these technologies are expensive (the real-time RT-PCR machine is only about $50–60,000 but the reagents are very expensive) or widely unavailable in the case of the FTMS.

Because of this, I believe that an infrastructure program that will support not only the initial costs of such equipment, but also such things as development and commercialization of the equipment as well as ongoing costs (e.g., reagent costs, technician time, maintenance costs, etc.) is the best way to ensure that the technologies reach their full potential.

Although I am not exactly sure of the mechanism for such support, perhaps a "genomics center" program designed to provide start-up and ongoing costs for a such a service-type center would be in order.

First, NHLBI should provide support for collection of samples in a wide variety of clinical environments including industry-sponsored clinical trials, new population-based surveys, and other environments. Since costs of analyzing samples are dropping rapidly, data collection should occur now while the infrastructure to genotype the samples in an automated fashion is developed separately. Regional genotyping contractors could be established to provide efficient core lab capabilities to all NHLBI investigators (with pre-negotiated rates-investigators can take advantage of this network or buy services on the market to maintain price efficiency among suppliers).

Consent and data-sharing procedures need to be developed to meet the requirements of HHS and FDA broadly (OHRP, HIPAA). Specific safe-harbors for following pre-specified procedures need to be created if this type of research is to move forward.

NHLBI should bring experts together to discuss and define uniform definitions of key clinical endpoints to be used in all clinical trials-- both clinical definitions/descriptors as well as key laboratory tests. These endpoints can then be used in all clinical studies funded by NHLBI so that a standard set of outcome measures is accumulated over time. Definitions should be updated at least twice yearly to incorporate new clinical information/studies. It will be important to continue using older tests as well in many cases for cross comparison between studies (e.g. CK-MBs and troponins in defining MI) over time. This would also help NHLBI know standardized costs for such tests since volume discounts could be negotiated by a few key national labs for all PIs.

a. NHLBI would provide a huge service if it would develop and provide data sharing platforms and standard web-based data entry vehicles so that PIs at different institutions (or even at the same institution) would be able to share data quickly.

b. Establish a uniform way to record the location of genetic variants in genes. If one searches the literature now, even key genes often give the location of a specific amino acid based on the cDNA sequence or from the initiator methionine at a protein level. The numbering system often varies from paper to paper or government database to database. Since most genetic variant analysis is performed on genomic DNA, this it is very confusing to use numbering from cDNAs, especially when upstream (5'?UTR, 5'-regulatory) sequence is analyzed. If the A in ATG is given as 1 for every "gene," then the variants can always be referenced from this point, both upstream (5', negative numbers) and downstream (3', positive numbers), and the numbering can often be cross-referenced to cDNAs and ESTs as well. The disadvantage is that this is not the site of transcription initiation, but it is uniform, avoids the problem of multiple transcription initiation sites in some genes, and makes analysis at least consistent between genes. Amazingly this has not been done in any private or government database easily available. One could start with a list of genes found to be important in CV diseases.

c. In terms of consenting patients, development of key wording for sharing DNA with other investigators and other studies (that is HIPPA compliant) would be helpful. The issue of de-coded versus anonymized DNA needs to be specifically addressed since it is critical that clinical data be updated over time (to obtain true outcome data) in order to be the most valuable. This could be the boilerplate upon which different institutions might add additional language, but itself would at least be HIPPA compliant.

d. NHLBI researchers need a facility that can make reliable lymphoblast cell lines for immortalization of DNA at a government negotiated excellent price. This is critical for the development of a large genetic/clinical database for use by many PIs now and with new genes in the future.

e. Negotiated prices for key microarray and protein chip analysis of tissues (where PIs could send the tissues off and have the analysis done) would lower cost and improve

consistency in data analysis. The critical issue for microarray data is the hypothesis-driven question, not the "technique" per se and having centers of excellence where the analysis is top rate would be invaluable for NHLBI researchers and would provide consistency in clinical trials that would enhance the final product.

f. Fund several data analysis centers (perhaps 5 or 6) across the country where investigators can send their genetic and clinical data sets for expert analysis. Provide salaries for groups of investigators at these cores, regular meetings between centers, and think tank environments for development of new approaches. Collaborations between database (NCBI) types and statistical geneticists and practicing physician scientists active in the area of clinical genetics should be encouraged.

Infrastructure for widespread high-throughput genotyping and haplotyping is needed. You are familiar with our collaborative work with Debbie Nickerson and the PGA at the University of Washington, but this resource is clearly limited. We still need to demonstrate proof of concept for this approach using data from population-based studies, such as CARDIA and CHS. Technologies that improve the characterization of informative phenotypes are needed. Advanced statistical methods also are needed to deal with large numbers of variables and to combine the genetic and environmental data. I'm not sure how much additional progress is needed in consent procedures. Optimal and timely use of population-based resources and data sharing are both needed and appropriate.

Importantly, the genomics approach will need to be examined in the future together with expression array data and proteinomics, as these newer technologies are further developed and applied to large study datasets. This is critical to determine what additional data is most likely to impact public health, and whether genomic, expression array, or proteomic data has the greatest utility in a particular situation.

For many large data are easy to share —the computer files are available , but without access to stored plasma and DNA and an appropriate consent form that allows sharing this is of limited utility. DNA and plasma are often limited and access is understandably difficult.

Bioinformatics is a major concern and need. Interpretation of genome and proteome-derived data is critically dependent on optimal analysis and thought should be given for infrastructure available to all grantees (and perhaps other) that addresses this problem.

Reasonable guidelines for IRBs should be established that define use of anonymized genetic samples. IRBs should be encouraged to follow these guidelines but good sense must be used in their formulation.

Population-based and patient-based studies are relatively labor intensive and time-consuming, yet collecting and collating such data is critical to subsequent work. In many instances, it is not possible to 'revisit' the source for repeat sampling. Perhaps there should be a central resource for establishing EBV lymphoblastoid cell lines and consent procedures could be streamlined.

I commend the NHLBI Programs for Genomic applications setting up the infra-structure of central resources.

Whenever possible, if there are ethnic propensities for certain mutations or phenotypes, these should be communicated through public health organizations who could help disseminate the knowledge to those ethnic groups.

In my view, publicly funded data should quickly be made available to any qualified investigator (I think the Seattle PGA is a good instance, and it's getting used).

The greater the fraction of common-use core resources, bioinformatic, statistical, molecular and data, the more investigators there will be who can think about or work on heart and lung problems. Focusing on core, widely accessible rather resources rather than those restricted to individual investigators is cost effective as well. More investigators with smaller parochial empires, rather than fewer with larger are, would in my view increase the odds of progress by a kind of ecological diversity of scientists and less commitment to status quo.

I would suggest strong constraints in regard to making things publicly accessible, as a condition of funding, and greatly restricted support for things that won't be shared. People will get used to it, if that is the only way they can get funded.

It would be nice to have a uniform set of genetic markers (SNPs or haplotypes), so that linkage could be found in many families. The resource of developing these disease related SNPs does better as a contract, rather than a PGA or R01.

RESPONSE 3: MONOGENIC FORMS

Consider and recommend approaches to applying genetic findings from rare monogenic forms of heart, lung, blood, and sleep disorders, such as long-QT syndrome or alpha-1-antitrypsin deficiency, to more common conditions such as arrhythmic death in coronary disease or chronic obstructive pulmonary disease.

I am currently doing this with the HyperGEN LVH study. We are finding genetic linkage in regions that contain genes for monogenic forms of hypertrophy. I believe what this means is that the same genes contribute to both conditions. Without family studies/linkage we may not have come to that same answer (i.e., had we relied exclusively on candidate genes. There are just too many possible genes to test).

Just this month, it was reported that homozygosity for mutations in the BRCA2 gene can lead to Fanconi anemia. Similarly, variations in the apolipoprotein E gene predispose to both increased cholesterol and Alzheimer's disease. Thus, researchers need to be aware that apparently rare mutations may have broad applicability for understanding more common forms of heart, lung, blood and sleep disorders, or at least other relatively rare diseases. Once again, collaborative efforts among researchers working in different disease areas may facilitate identification of such susceptibility loci.

Findings on monogenic diseases—such as Familial Hypercholesterolemia—may aid in clarifying mechanisms of disease, in this case the role of the LDL receptor. Such mechanisms need subsequently to be investigated in appropriate study populations.

I simply was concerned at the stated intent to focus efforts on common diseases, and to de-emphasize rare disorders. I may have misunderstood, but I want to make it clear that studying rare disorders can provide vital information for common pathological states. For example, chronic granulomatous disease, CGD, occurs in only 4/million individuals. However, CGD has provided vital clues to the NADPH oxidase, one of the key enzymes used by the body to combat infection inflammation, etc.

Create a registry containing all genes from the literature from animal and human studies that have been reported to show association or linkage with hypertension or related cardiovascular disorders. It should state also which genes were found to be linked/associated in certain populations, but not in others, which genes were suggested to be relevant to certain phenotypic characteristics and it should also include negative findings.

You should not leave out familial hypercholesterolemia. Several countries (Netherlands, France, Belgium, Spain, etc.) offer medical care or treatment subsidies or discounts for genetically verified familial hypercholesterolemia. The U.S. is notably behind other countries in attempts to help those at very high risk or mitigate the potential disparities in insurance coverage that could result from discovery of very high risk conditions. FH is far more common than other well defined genetic conditions leading to increased cardiac risk (long QT, cardiomyopathies, etc.) A common problem for all of them is the lack of clinical laboratory services to identify the mutation (or diagnose whether a mutation is present) if a clinician suspects the problem. Rapid, reasonably priced laboratory diagnoses of well defined genetic disorders would be very useful.

The rationale for a such an approach lies in the relative proportionate mortality of these rare Mendelian disorders with respect to the broader definitions of arrhythmic death or COPD.

Understanding the link between genetic mutations and pathophysiology is an excellent approach. For example, understanding the link between the genetic mutations associated with long QT syndrome and sudden cardiac death would be extremely valuable in helping us understand vulnerability to sudden cardiac death associated with other cardiac disease such as heart failure.

This question strikes at the heart of the perception problem. Simple monogenic disorders, which we recognized when I was a medical student, are uncommon. While we can learn form that experience, public health problems are mass diseases associated with aging and long-term exposure. There are undoubtedly genetic components to these diseases but these factors are most likely to be polygenic, involving many genes, and have significant, if not dominant, environmental exposure effects. Interaction of genes and environment are the action sites in the coming years. Monogenic disorders may provide insight and understanding, but the serious chronic diseases which affect the United States population are not attributable to monogenic disorders.

As mentioned above currently available genetic information that impacts on patient care needs to be applied to patients both to improve care and as a proof of concept that shows that public resources are being well spent. All it will take is saving a small number of lives because of improved diagnosis through genetics to convince the public and Congress that this program is paying dividends.

One obvious method, sometimes but not always effective, is to look for polymorphisms in the rare-disorder genes in common disorders. Promoter polymorphisms or protein changes might change risk for common diseases. Screens for interacting proteins may similarly yield helpful results.

This approach is already being used in a number of candidate gene studies.

We are still in the data-gathering stages; I don't feel that we can with confidence apply genetic findings to more "common" arrhythmic death in CHD or COPD—the latter two being much more complex.

Use genes discovered from rare, devastating mutations to guide resequencing of the entire gene in more common complex diseases which use the same physiologic pathways. By resequencing consistently, less severe genetic variants will be found that may be more common and therefore important. Funding of studies to take each of these variants and study them intensively in the laboratory (with mice or with human cDNA mutations to test biology) is key and NHLBI can have databases available to all PIs with this information. This is not available in a cohesive fashion now.

You are familiar with our collaborative work with Jeff Towbin, using material from CHS and our population-based case-control study of cardiac arrest in Seattle. The jury is out on whether this will be help inform public health efforts related to the prevention of sudden cardiac death in the community.

Rare monogenic disorders may have little to do with herterogeneous common conditions. One approach is to look for SNPS in the genes affected (since the genes have already been shown to be key) and see if genetic variation in these genes alters risk or outcome of common conditions.

I think there is ample precedent from studies of rare conditions, e.g., some forms of hypertension and cancer, that suggest approaches to more common forms of a disorder.

It is becoming clear that almost all monogenic diseases have quite variable phenotypes. Thorough analysis of patients with unusually mild or severe disease and their family members often shed clues on the modifier genes. Identification of these modifier genes can prove extremely difficult and seems to the ‘block’ in translating such clues to clinical application.

The problem, in my view, is our deeply embedded belief that this is what we can do. But suppose findings and methods that work with strong effects simply are inappropriate for weak effects? Then, no amount of meta-analysis or scaled-up technology will suffice.

Maybe genetic analysis simply will not explain or predict common chronic states the way we have come to expect from our successes in the ‘mendelian’ subsets of things.

If so, we are simply throwing money away for almost no real yield by continuing to invest in this type of approach.

I know this is an unpopular view, but the very fact of this questionnaire probably reflects the frustration we've had with business as usual.

I would like to see comparative genomics rise to the top of the chart here. There are excellent genetic models—mouse and zebrafish. We need a comparative chromosomal chart to evaluate the function of genes that come out of the association studies for multigenic traits. This is database building and will really help. this would include syntenic relationships to mouse and zebrafish mutants, and a gene expression database that shows in situ hydridization of orthologs.

A concensus conference could define a short list of potential disease genes. SNPs could then be found in those genes, and made uniformly available. Again, it is better to have a contract approach to this work, since it is a resource.

RESPONSE 4: TAILORED INTERVENTIONS

Please suggest approaches for using genetic information to enhance the effectiveness of preventive and therapeutic interventions by tailoring them to patients or population subgroups. Similarly, consider approaches for using genetic information to reduce the frequency of adverse drug reactions and suggest strategies for implementing these approaches.

We need to understand how genomic variation contributes to common conditions in the population and how genetic variation predicts treatment response. There are currently several pharmacogenetic studies doing this. It would be interesting to focus on family designs/linkage in the pharmacogenetic realm. That may point to new pathways/modes of treatment.

If, as is probable, there is selective gene-based response to certain therapies, then benefits and or complications can be tailored with this in mind. An example would be aspirin resistance. Approximately 5-20% of any population may be relatively aspirin resistant. Since these patients are not delineated prior to most studies, it may be that the benefit of other non-ASA drugs in cardiovascular drugs may be much larger in these ASA-resistant patients and that the side effects, in turn, might be less if aspirin were excluded from their regimen. By tailoring medications for each patient, either by increasing drug levels for those with diminished effects or by drug discontinuation for drug non-effect, the general population as well as the defined population would benefit.

We have no specific comments on this section. The example of 'Paracetamol' (fast vs. slow acetylators) shows that issues of intrinsic resistance and sensitivity may be important.

Initiate pharmacogenetic studies aiming to find relationship between antihypertensive response to specifically acting tools (e.g. angiotensin AT1 receptor antagonists or b-adrenergic blockers or a2-adrenergic agonists, etc) and genotypic profile (e.g. allele variants, SNIPs, etc.) of the target receptor or mechanism. Correlate with biochemical profile (angiotensin II levels, catecholamines, etc) and clinical characteristics (e.g., salt sensitivity). Tap into the resources of large outcome studies, where a highly specific intervention protected some individuals but not others: For example, in the LIFE study, compare genotypes of AT1 receptor, AGT, ACE, etc in patients who did versus those who did not sustain cardiovascular episodes. Such outcome trials exist also for ACE inhibitors in hypertension or diabetes, for b-blockers in heart failure. Additional such studies can be encouraged for a2-adrenergic agonists and other modalities.

There are many ideas that could be suggested here—most involve more vigorous treatment of standard risk factors, essentially. A few examples may arise for specific disorders (like avoiding vigorous exertion or using a beta-blocker for those with long-QT, etc.).

There are presently numerous examples in the literature of associations between genetic polymorphisms and drug efficacy or toxicity. Understanding the genetic contribution to variability in drug response also has the potential to markedly improve the safe and effective use of medications. However, several important strides forward need to be made before this type of information is useful in the clinical setting. First, most studies to date have focused on single polymorphisms in single genes. Given the complexity of the drug response, and the signal transduction cascade involved in most drug responses, this approach must become more sophisticated, and take into account numerous genes that might be involved in the drug response. Given that the pharmaceutical industry is generally frightened of the impact of pharmacogenomics on "the blockbuster drug", NIH must take the lead in support of research in this area. Additionally, studies will need to be conducted that document that genetically-guided therapy is superior to current approaches to treatment, and again the funding for this will need to come from NIH and other competitive sources, as it is unlikely to come from industry.

In an issue related to the question below, pharmacogenetics also has the potential to increase adherence to therapy, particularly in diseases like hypertension. Presently in hypertension, treatment is by a trial and error approach. Because the first (or second) drug tried may not control the hypertension, patients often become disenfranchised with the process and stop all treatment for their silent disease. Pharmacogenetics has the potential to result in better identification of the most appropriate drug the first time, which could lead to increased adherence to therapy, which in the long run could reduce the consequences of longstanding, untreated hypertension. If studies could document these adherence issues, the use of genetic information to guide therapy would be that much more important clinically.

By analogy, consider the case of salt-sensitive hypertension. Salt-sensitivity has a much greater prevalence, regardless of hypertension status, in African Americans compared to Whites. Tailoring an educational campaign for salt-reduction in the diet for African Americans thus makes sense and may even represent a more cost-effective expenditure compared to a campaign to target all Americans.

Developing an African American panel of genetic tests to determine the best treatment for hypertension and another panel for Asian Americans, and so on, may well result in a faster route to hypertension control.

The question of using genetics to "target" individuals, specifying their unique needs, is an attractive and commonly held one. Research to find out which therapies (e.g. medications) are more effective in certain individuals is likely to be productive. Unfortunately, the pharmaceutical industry has begun to lose interest in the 'targeting approach' as it splits markets forcing them to develop more specific and unique medications.

At the wider prevention level, I am concerned about the potential for labeling of individuals as susceptible or high-risk when there is no obvious treatment. I am also concerned about reassuring individuals that their health-impairing behaviors are harmless. For example, some

people (probably very few) can smoke two packs of cigarettes a day and have no harmful health effects. I believe they are genetically protected and rare, but this thinking sends a message about the need for mass screening and the potential for some people to engage in harmful behaviors without concern for their health. I believe we should look first at methods to use genetics to more effectively target individuals or population subgroups for alternative treatments. We should not be looking for good or bad markers when treatment options do not exist.

I propose collecting data and DNA from thousands of patients in failed clinical trials and using a genome approach to identify genotypes of non and adverse responders as well as positive responders to common and simple therapeutic interventions—e.g. antiarrhythmics—identify genotypic markers that can be used to tailor therapy—same for heart failure—I would focus on these two as the number of patients is the largest—and by partnering with companies that can provide high throughput genotyping using SNPs etc rescue therapies that have been shelved because of adverse side effects or increased mortality by culling out the non responders and adverse responders leaving populations of patients that do respond.

My bias would be that EVERY therapeutic trial at phase II or phase III should have a pharmacogenomic arm, storing whole frozen blood or DNA from same, to evaluate polymorphisms in case of untoward effects or unexpected pharmacokinetics. It is much easier to collect such data prospectively, then analyze as the patient numbers reveal themselves.

This approach holds great promise if we have a single payer health care system. In the absence of a single payer, more genetic information may open the door for more discrimination—just like having an existing illness does.

Within clinical trials, case-only studies provide valid, efficient, and unbiased estimates of drug-gene interactions. White cells should be stored in all trials so that these questions can be asked. For rare severe reactions such as valvular damage from fen-phen or liver damage from troglitazone, which are likely to represent undetected drug-gene interactions, it would be terrific to have a method of obtaining white cells from these case report studies. For historical, evolutionary and clinical reasons, my own work focuses on drug-gene interactions as an example of the broader category of drug-environment interactions. My views here are not disinterested. New placebo-controlled trials might be appropriate. For instance, if low-dose diuretics reduces the risk of CV events in those with the adducin variant, perhaps 25% of the non-hypertensive population carries this variant and might benefit from treatment with low dose diuretics--a question that could be addressed in a placebo-controlled trial.

Pharmacogentic information is unlikely to be developed rapidly by industry. NHLBI should provide resources to begin to address questions of drug-safety (relationship between metabolism (P450), polymorphisms, and efficacy). NHLBI could develop a mechanism to enable investigators to piggy-back these efforts to industry sponsored trials as well to provide a public database to answer questions about safety and efficacy of pharmaceuticals.

I wish I could....I guess I am too cynical at this early stage in our data gathering. Sorry, but I don't believe we can extrapolate yet.

We are obviously looking today to discover genetic variants that influence diseases or drug responses to diseases. We must do this (as discussed above) before we consider how this information can be best used in stratifying patients into specific outcome categories designed to optimize their therapy. This question therefore cannot be specifically answered today, but is the final goal of genetic studies.

As you know, the use of genetic information to enhance the effectiveness of preventive and therapeutic interventions requires large samples sizes, with both genetic and environmental data. Large, multi-center, surveillance systems for both outcomes and exposures (genetic and environmental) are needed. One set of environmental exposures that are likely to interact with genetic variation are commonly used drug therapies. As noted, this work might focus on cardiac safety as well as cardiac benefits.

A science -base approach is needed; i.e., clinical trials. Showing a gene does "x" does not mean that in the clinical arena this effect on x will be relevant. There are many examples.

Pharmacogenomics has promise for identification of susceptibility to adverse or favorable reactions to a drug. Knowing this, simple means of screening patients could be devised.

The incidence of peripartum cardiomyopathy in young women varies regionally. In the U.S. an incidence from 1/3000–4000 has been reported. However, in other countries, e.g., Haiti and certain regions in Africa, an incidence of 1/300 and higher have been seen. Although etiology of this unique form of cardiomyopathy, which targets mothers within one month before delivery to five months post-partum, has yet to be defined, an autoimmune basis has been proposed. A unique approach using genetic information to address this issue might be to develop computerized genetic and genealogic databases of identified mothers with PPCM in local areas with high reported of this disease. This information could then be used in linkage analysis studies or with high density microsatellite genotyping among family members to define specific alleles or haplotypes that may be associated with this disease. This information could also be compared with other disease associated immunologic phenomena, e.g., presence of cardiac specific autoantibodies, to help further characterize possible underlying autoimmune mechanisms that may be involved. Such information may ultimately be used to develop highly sensitive and specific screening assays for predicting this disease and may lead to new strategies for prevention and/or safer pregnancies.

Until we know if certain population subgroups are more prone to certain diseases due to underlying genetic variability, it is difficult to introduce preventative and therapeutic interventions. Again, until we know if certain sub-populations are prone to adverse drug reactions, it is not possible to implement any interventions. Perhaps the NHLBI could commission risk assessment studies on use of certain drugs to start with.

In the last box, I'll address what I think the real issue is. Here, I'll say just that until we really understand cause and risk, and accept their realities, prevention and intervention will continue to grope and meander.

Prospects for progress in relation to drug reactions are a bit better, at least for drugs whose targeted pathway is well known, focused, and properly understood. Then, it's a study of very specific pathways which is just what our scientific methods are designed to deal with. Of course, to the extent (probably considerable) that humans are laden with protective shunts and alternative pathways, this too will be frustrated.

It is now possible to do drug suppressor screens in zebrafish. With a mutant in a particular gene, drugs could be found that rescue the disease phenotype.

Gene therapy is obvious.

RESPONSE 5: ADHERENCE

The possibility that an individual's knowledge of his/her own high-risk genotype could improve his/her adherence to interventions is intriguing, but has yet to be investigated. Please consider the potential importance of this area and suggest approaches to determining the impact of genotypic information on adherence to interventions by an individual or his/her family members.

This is too far in the future to invest in currently. A few studies have been done that show that genetic information re: common diseases does not really motivate behavior change.

This is an important area of research that is just beginning to be addressed by researchers in cancer. For example, studies examining women's attitudes towards testing for BRCA1 and BRCA2 mutations are ongoing, and could provide new insights about effectiveness of prevention strategies based on such knowledge. Because this type of information applies to relatives as well, family-based intervention strategies might also be effective. As our understanding of genetic susceptibility grows, social scientists and economists need to be engaged in order to determine whether knowledge of high-risk genotypes is a feasible component of an effective and cost-efficient intervention strategy, either in clinical or population-based settings.

It is widely believed that an acute thrombotic episode can also depress levels of these proteins. This has led to the general practice that one does not measure these levels, if deficiency is suspected, soon after presentation with an acute thrombus. Although a widely held belief even by experts, there is little evidence to suggest that this is fact true and this becomes an issue in the scenario of patients who are less that totally adherent and who may not follow up. If testing these patients yielded an "at-risk population" who were then advised of the potential risk and the need for repeat testing and good adherence, I think that this would more than balance the minor differences that might be seen in protein C and S and antithrombin III deficiency after the completion of the acute thrombotic phase. Furthermore, if tested immediately and one finds normal levels, one can be sure that the protein deficiency does not exist.

The current evidence suggests that providing people with DNA derived information about risks to their health does not increase motivation to change behavior beyond that achieved with non-genetic information. For some people genetic information may even reduce motivation to change behavior. Genetic information could facilitate behavioral change if people are offered effective risk reducing interventions that are tailored to their DNA based risk, as could be the case for smoking. This, however, is likely to be the exception for the foreseeable future. People's motivation to change behavior may be increased by strengthening two sets of beliefs: firstly their beliefs that changing behavior can reduce risks and secondly, their beliefs in their ability to change.

The same group is carrying out a randomized trial of the cognitive and behavioral impact of providing DNA-based risk information to relatives of parents with familial hypercholesterolemia.

The possibility remains that individual knowledge of high-risk genotypes could improve OR REDUCE adherence to interventions to reduce modifiable risk factors. It could also motivate individuals to initiate, adhere to, or abandon dietary and life style habits that are not targeted by an intervention but for which there is ample patient education. These responses to high-risk genotype information should be examined in cross-cultural settings and in relation to comprehension of individual versus population-associated risks which are carefully communicated to individuals and to ethnic groups with a higher prevalence of the implicated genotype. The return of genotype information to individuals should be accompanied by information on modifiable risks and evaluation of this information could be done by assessing the risk behavior and immediate outcomes such as blood lipids, markers of tobacco use, blood pressure control, measures of obesity, and diet both before the return of genetic information and after its return, along with an assessment of the individuals understanding of their genotype. These changes, if any, could be compared between individuals receiving information on both positive and negative high risk genotypes.

Actually, there was data presented regarding genetic diagnosis of FH and subsequent adherence to lipid-lowering therapy at the International MEDPED meeting in Austria (July 2002). The research was conducted in England.

The confirmation by genetic testing of the enhanced risk of CVD and the positive impact of dietary, and/or lifestyle, modification to reduce both morbidity and mortality starting at an early age is promising. Now would be the time to prepare a prospective study along the lines of the Framingham study but for a more racially diverse set of outcomes.

In the sleep disorders, knowledge of genetic susceptibility, either to circadian rhythm sleep disorders or to short and long sleep, would be very helpful in patient counseling and organizing treatment strategies.

I don't think genotyping (just another risk factor) would help adherence. Smoking is a high risk factor yet people still do it.

This is an old health education belief. There is a subgroup in the population that is highly motivated by information on their health status and who will take aggressive action to change their behaviors. They tend to be highly educated, affluent and have a long-term prospective on the potential for their lives. Health professionals have a high percentage of these individuals. Unfortunately, they are not that common and certainly do not represent the majority of the population who present with most of the disease. This remainder and majority are the poor, minorities and most of the middle-class. Already, more than 2/3 of the population with high blood pressure do not take medication despite identification of the problem, available treatment and widespread knowledge of its harm. I suspect that identification of genetic abnormality will not lead to improved health behavior, but denial and avoidance. I wish I could be more optimistic but experience suggests otherwise. Self-knowledge is not a very strong motivating factor for most people. This is demonstrated in many health education studies.

We know for some dominant genotypes (familial hypercholesterolemia due to LDL-R defects) that advance knowledge improves adherence in some families but not all. For recessive genotypes, there is little information that knowledge of thalassemia trait or sickle cell trait modify behavior of teens, but do affect reproductive choices for some.

For risk factors, there is so far no data to suggest that early knowledge of factor V Leiden affects health behavior very much.

A trial of about 2000 Caucasian 10 year olds would yield 100 factor V Leiden carriers. It might be possible to follow this cohort for a decade or two for choices about smoking, contraception, and clinical management.

The alternative hypothesis may be just as likely in some cases--a fatalistic response that vitiates adherence. Clearly, we need more work here, including the "family" effects of genetic testing.

This is a very important area. Data are available from studies of patients with Huntington's disease and BRCA1/2 for models of treatment choice (as well as HIV). However, data may not be available for broader population responses or for important subgroups of the population.

I believe regardless of the emotional factor that familial analysis, such as prostatic cancer as done by Dr. Offitt at S-K in NYC, is very valuable. True, there is little one can do with the information that you may in a high-risk category...But, e.g., again with prostatic cancer, frequent CAT scans, can reveal a very early CA, which is amenable to surgery. One never knows when a breakthrough occurs, so a knowledge of being in a high-risk category is appropriate.

Bring together unusual groups of people (behavior scientists, systems experts [e.g. folks who enter industrial plants to change behavior to decrease accident rates], and public health experts) to discuss how to best modify behavior in high risk individuals.

a. Educate the public on the benefits of knowing if an individual is at high risk—e.g., whether exercising is safe or risky, whether a drug should be used, or whether certain genetic patterns suggest preventative therapy in the absence of symptoms. The reality is that in common complex disease, genetic information is less risky to know than your lipid levels perhaps. Yet the public is still hearing discrimination messages almost uniformly whenever genetics is mentioned. Get out the positive, practical message to the public in a very carefully targeted way to improve health. Partnering with AHA in this regard may be helpful.

b. There are some ongoing studies in this area-use their information since a couple are close to finishing.

So could taking estrogen (until this year); i.e., prove the effect first then see if can alter behavior—don't rush to the population with half-baked data.

Of course this is important but even with knowledge, changing behavior is difficult. Behaviorists and social scientists must get involved for this to be effective.

The prospects of identifying specific genetic patterns or phenotypes associated with autoimmune forms of PPCM suggest the possibility for developing screening tests that could provide valuable clinical information which could be in conjunction with family planning to prevent the development cardiomyopathy during the peripartum period. Preliminary evidence suggests that the risk of PPCM increases with parity. A genetic profile for high risk in conjunction with other screening tests, e.g., serologic tests for the detection of PPCM specific autoantibodies, could potentially provide the means for preventing high-risk pregnancy associated cardiomyopathies in mothers.

Some individuals would rather not know if they have a high-risk genotype, as this could have implications for health insurance, etc.

We know that this is probably mostly nonsense. Behavior modification for well known risk factors, and compliance with clinical or preventive measures, is known to be frustratingly poor. People still smoke, and it requires no technical knowledge to understood its mortal risk. Responding to one's own genotype would expect far beyond what most people are able to understand—even, probably, most biomedical people.

But the core issue again is that we are so poor at understanding risk, that providing risk estimates or behavior suggestions based on genotype would verge on the morally indefensible. We all know this very well.

Genotypic information will be most useful for the a small subset of very high risk individuals (like carriers of the major BRCA1 or LDL Receptor mutations), and they already should (or could) be under clinical care and advice.

Putting this burden on individuals is like saying each ordinary person can manage his/her own retirement or health care investments or stock portfolio. It is a program for social disaster. I think we know that this is so only for a few people with education, knowledge, and the like. To ask it of genotypes, for which understanding of risk is crude at best in most cases, is asking a lot, and asking for a lot of trouble.

Finally, if risk chips (forgive the pun) become too widely available, a likely consequence will be the discriminatory use of them by all sorts of people (perhaps including family members), and will involve employment, school assignments, health care, insurance, and civil rights. Why pay the cost to send a kid to school whose risk chip says s/he's going to get cancer?

Of course, these other 'users' won't understand risk any better than professional geneticists do, or clinicians. But we're in a deterministic age in which people believe they understand and are willing to act on it, and that is the danger of a too-sanguine approach to knowledge of 'risk'.

RESPONSE 6: SCREENING

Please recommend strategies for using genetic information to identify patient or population subgroups at high risk of heart, lung, blood, and sleep disorders, including criteria that might be used to determine which genetic variants to screen for, and in which subgroups. Please suggest how additional information needed to determine such criteria could be obtained. Suggestions are also needed on which screening approaches to use and when (such as population-wide vs. targeted or high-risk groups), and what information to provide after screening.

This is hard to do currently since there are very few genetic variants in CVD that have a high enough attributable risk to warrant screening. Some examples that may be important based on some preliminary work:

apo—dyslipidemia
Factor V—OC/HRT use
PlIIb/IIIa—restenosis post stenting

In addition to the traditional population-wide and high-risk intervention approaches, one alternative that has recently received attention is "family cascade" screening. Familial hypercholesterolemia, because it is primarily a single gene disorder, provides a useful illustration of this approach, in which the "population at risk" is relatives of heterozygous probands with known FH. By definition, 50% of first-degree relatives of such a proband will have an FH mutation that can be effectively treated by lipid-lowering therapy to reduce CHD risk. Studies in the Netherlands and the United Kingdom have shown that such screening strategies are feasible are cost effective and have the potential to prevent half of CHD death among relatives. As more susceptibility mutations are identified, and modifying factors are understood, this intermediate approach may be applicable to more at more families at high risk for disease.

At the same time, knowledge about the role of mutations in disease susceptibility raises difficult issues about information to provide to population groups after screening. A recent study suggests that, at least in a research setting, study participants wish to be informed about such genetic information, even if its meaning is uncertain. As a result, public health professionals need to be prepared to provide such information, including the involvement of genetic counselors when appropriate. Further, because genotype results, by definition, provide information about family members, the application of genetic knowledge to populations needs to take in to account the implications for relatives. Again, cultural and ethical views of such information may vary dramatically in different population groups.

Building a registry for people at risk of heart failure:

It has become apparent that up to 30% of patients with dilated cardiomyopathy may have family members similarly involved (Baig et al., JACC 1998, 195. Grunig et al. JACC 1998, 3:186). Although our understanding of the phenotypes of people with "familial" cardiomyopathy is still

in its infancy (Hershberger et al.. J Card Fail 1999, 203), much effort is needed to develop effective ways to identify people who have strong predispositions before clinical heart failure develops. It is likely that SNPs or clinically silent mutations in the majority of people may have important consequences upon development of heart failure. This could be either for prognosis of the course of disease progression or for response to therapy. It is important to note that compared with the prevalence of coronary artery disease, cardiomyopathy is relatively uncommon, although the incidence is increasing. Therefore because of the sample size in registries such as Framingham or Olmsted County, information derived from population studies may be limited due to the relatively low prevalence of this condition. A search for genes influencing premature and subclinical cardiomyopathy susceptibility among sibling pairs and related individuals may therefore be suitable, and likely to be more successful in a cohort design rather than case-controlled study. An NIH funded multi-center data base, including a large number of heart failure centers may be needed. Genetic screening beyond obvious structural gene candidates will also be necessary, as genetic alterations in cardiac metabolism (especially in the diabetic population), or rhythm abnormalities may have important impact in disease progression.

For "proband" individuals, the natural history of the disease should be carefully investigated—not only "etiology" but also the timing of progression, responses to therapy etc. We emphasize that only with a large sample size (thousands), will patterns of phenotype emerge. Genetic variations may also be compared between those affected and non-affected sibling pairs at different times (i.e., sibling pairs that do not have disease may develop cardiomyopathy say 5 years later). After such a "registry" for at-risk siblings is obtained and genetic information extracted, careful documentation of cardiac status (by sequential systolic and diastolic assessment as well as cardiac dimensions), functional and neurohormonal status, and risk factor development over time may yield valuable information. Other potential cohorts would include patients with risk factors for developing cardiomyopathy—poorly-controlled diabetics or hypertensives, patients suffering from viral syndromes, alcoholics, etc.

In this large cohort, our ultimate goal would be to search for variations in expression of genes that predict heart disease. Given the fact that cardiac biopsies will probably not be available, the most practical alternative would be to measure levels of one or more marker proteins (similar to ANP or C-reactive protein, HSP 60, etc) expressed in the heart but secreted into the extracellular milieu. From gene array studies, it is clear that several genes with altered expression in human heart failure encode proteins that are secreted (see Yang et al., Circ 2000, 102:3046–52,2000; Tan et al., 2002, 99:11387–11392). It is also anticipated that gene expression studies of novel ESTs may provide novel circulating biomarkers for heart failure. (We have recently identified ESTs which are expressed at a similar level as ANP in failing human hearts but only at very low or undetectable levels in non-failing hearts—some of these may encode secreted proteins). Thus we would expect that blood samples will be the major source of material for study and identification of altered levels of circulating factors in at risk people.

It is essential that WHO or similar screening criteria be applied in this field as in any other. It seems that for the next 5-10 years that new and useful findings will be heavily weighted towards mechanisms rather than to the direct application of screening. Replication of effects in different studies e.g. cohorts, is a key aspect of generating reliable functional genetic knowledge.

These questions anticipate that we are in a position to answer them at this time. I think, for the most part, this assumption is premature. We are perhaps at a stage to begin a public discussion on the need to consider population-wide screening and the counter-balancing option of high-risk group screening and to begin consideration of developing the criteria to decide between these two options. There is a need to educate practitioners and patients alike that genetic variants in the context of common complex diseases, such as hypertension, represent increased statistical risk not deterministic guarantees of morbidity and eventual mortality.

Eventually, it will probably be possible by testing a few dozen SNPs to determine a person's susceptibility to circadian rhythm sleep disorders. This information will be crucial in planning life-long treatment strategies for these chronic conditions. However, first the knowledge base of which SNPs cause these susceptibilities must be developed.

The information that we have at present should be targeted to high-risk groups where the yield is likely to be substantial. That means that few people will be eligible for screening.

If broad screening is contemplated, and the future suggests this, the recognized and published criteria for screening should provide guidance. Among characteristics of good screening practice is prevalence, false positives, false negatives, costs and, most importantly, the availability of affordable and effective treatments.

See response #4—again I would focus on heart failure and sudden cardiac death as there are large numbers of patients and little or no useful pharmacologic therapy for either disease.

Family studies, to identify familial concentrations of disease states, are the best way to accomplish this. Biased studies (recruitment of highly affected families) have been very effective in cancer genetics. Unbiased studies need to be larger, but might be better for common genotypes.

Broad screening in the physicians health study and nurses health study need to be reproduced in the population at large.

Universal screening is not an effective science tool, I believe.

We are not yet at the stage of implementation though a consideration of criteria is a lovely idea. The criteria for screening generally include accuracy, reliability and an available form of treatment. I supposed that information about prognosis could count. While we can measure genetic variation accurately, findings need to be replicated in similar populations and in other populations before screening can be considered. The NHLBI could take a lead here in developing and promulgating criteria, which are likely depend on the context and patient preferences.

Research should include patient assessment of risks and benefits of screening. This includes how patients process information in the non-risk, high-risk and secondary prevention periods (which may differ).

It's not clear that we have trained practitioners to provide counseling about uncertain genetic data. Research on methods of counseling and teaching this subject are urgently required.

Add genetics to all the ongoing clinical trials-but this is not enough. Additional clinical endpoints (perhaps a battery of 10-20) so that while each clinical trials has its own endpoints, there is a common core of cardiovascular/renal/CNS data collected that everyone can use. Also plasma/tissues also needs to be stored for future use. Standardizing clinical outcome definitions is absolutely required for this endeavor (see above).

Integrate multiple approaches in determining candidate genes-physiology, drug intervention pathways, microarrays, expression data, association studies, etc. It needs to be an integrated approach.

It will be important to not only assess the main effects of genetic variation, but also the interactions of genetic variations in candidate genes and pathways with known environmental determinants of cardiovascular diseases. In short, merely showing that variation in a gene or pathway doesn't contribute independently to risk assessment is not adequate to explore the potential utility of this data in risk stratification and in understanding potential mechanisms that underlie complex phenotypes. In short, the impact of genetic variation on complex phenotypes should be evaluated in the context of known demographic and environmental risk factors.

Clinical trials needed.

The criteria that should be used for screening should be based on clearly defined phenotypes, ideally using a biochemical, protein or DNA assay as the procedure can usually be scaled up for high throughput screening. Dried blood spots as starting material would be most appropriate as it is easily transportable and allows screening to be centralized. It is better to err on having more false positives than negatives as suggestive results should be checked in second line testing using fresh material and different techniques. There should then be an infra-structure in place to trace the affected individuals and their families with offer of genetic counseling services. Obviously, one has always to balance the cost-effectiveness in such screening approaches. Whether it should be targeted to high-risk groups or universal, depends on the demographics and population movements. In a country like the US, one may have to resort to universal screening as it is such a melting pot of ethnic groups.

We really need a robust and rapid method for SNP detection and genotyping.

RESPONSE 7: POPULATION STUDIES

Please suggest approaches for utilizing NHLBI's large body of population-based observational studies and clinical trials to enhance public health applications of genetic information, including barriers encountered or anticipated and approaches for dealing with them. Brief descriptions of these studies are available at http://apps.nhlbi.nih.gov/popstudies/.

You need to provide the current investigators support to accommodate the requests. It requires too much attention at the "proposal" level when approached by people wanting to collaborate. They have no support for you and yet you have to spend time with them sharing information, etc., in order for them to write their grant.

In my view, approach has to be problem oriented and done by investigators that have interest and passion on the particular problems.

For example, I am a cardiovascular investigator who are interested in restenosis, smooth muscle cells, apoptosis and cell cycle regulations. I would be excited to put together a program that would address public health applications of genetic information associated with restenosis. But, I would be reluctant to do the same for hypertension or valvular heart disease.

NHLBI should come up with RFA that seek physician-scientists who have expertise both in clinical and bench research to develop comprehensive program to (1) archive the knowledge made available through population-based observational studies and clinical trials, (2) develop educational materials to clinical/research colleagues and patients and public in general, (3) generate hypotheses based on (1), and (4) actually conduct clinical, translational and basic studies.

For example, RFA can be set up so that 5 awards would go to investigators who will address atherosclerosis related issues, 3 awards to hypertension, etc, according to national interest and leadership opinions within NHLBI.

Alternative is to fund institutions in a form of the supplement to SCOR type grants.
Still another alternative is to create a career award type grant to nourish and build a group of mid-career physician-scientists who will be leaders of specific areas of cardiovascular medicine in terms of developing a comprehensive health care policy on the specific areas. For example, NHLBI can select 20 qualified physician-scientists and support them for 5 years with generous salary grants. These 20 investigators will be required to meet several times a year for brain-storming and even for didactic learning. These investigators will work with NHLBI to address specific problems associated with (1)–(3) mentioned above.

Principle is that (1) physician-scientists who are interested in specific areas of cardiovascular medicine are best suited for this type of task (2) since there are not many physician-scientists in this money drive society, NHLBI should have active efforts identify and support them in forms of RFA or creative career grants.

Existing population-based observational studies and clinical trials will be most useful for furthering the understanding of genetic information if DNA samples and hence genotype information are available on the subjects. Recontact of subjects for DNA collection from studies with valuable clinical and phenotype information should be considered. As genes or specific gene variants are identified a core facility could perform standardized genotyping. These existing phenotypic and clinical databases coupled with new genotype information could enable the evaluation of the role of a gene in various ethnic, age, geographical, population, clinical subgroups, etc. Such delineation of a genetic effect in these different groups will be critical to applying genetic research to the population based level.

I think the model for accessibility ought to be that of the CDC's for NHANES III, namely, distribution via ftp download. With genetic data, there is the concern of confidentiality. This can be approached by PKI transmission of data after a PI has signed a document returned by fax confirming agreement with terms and conditions set by NHLBI.

In my opinion, to the best of my knowledge and belief, the timely access to NHLBI-sponsored data collections is greatly impeded by having to obtain approval from the contract sites, such as Boston University for Framingham data, and/or arrange for a contact "co-author" at these sites. I don't believe that the US taxpayer is getting the biggest bang for the buck by the hoarding data. I do, however, agree that the contract site deserves a chance a first authorship as a reward for collection of the data but after a suitable time frame has elapsed, I believe that the data ought to be made easily and quickly available.

Many thanks for the opportunity to comment on these important issues, especially from one so junior. On the other hand, I have 5 years of experience with Canada's federal government in progressive positions of responsibility and 1 year on exchange with the U.S. federal government.

One of the most exciting scientific advances of the field of genetics is the willingness of many researchers to share their findings and data in a timely and efficient way. Research advances require the discoveries of many scientists and the current publication system limits dissemination. NHLBI should encourage rapid and widespread dissemination of genetic discovery.

The countervailing force to this is the increasing proprietary nature of genetic information. People who seek to patent and license genetic information will inhibit and delay understanding more than help it. Widespread and ready availability of research supported by NHLBI should include rapid and effective dissemination to all scientists.

This is an extremely important issue. I have an idea that genetic information from failed therapeutic trials should be used in genome surveys (e.g., SNPs, etc.) to identify genotypes that predispose to adverse reactions of lack of beneficial response. The concept is that many more clinical studies would be positive if target populations for a given therapy could be identified by genotype. Another way or saying this is that if you exclude non-responders and adverse responders on the basis of genotype - you would be left with a populations of patients form whom a given therapy works—by excluding the non-responders you can uncover those who should get the treatment. The genetic information including DNA would have to be made available to companies and consortiums able to perform large scale genome surveys that could then be matched with clinical databases to identify the genotype-phenotype correlations. This would be a way for the NHLBI to maximize the benefit to patients from the really large clinical trials—especially those that are stopped because of adverse outcomes or lack of benefit to patients.

The idea is nothing new, and you may even treat my comment as being unresponsive to the notice below. But, nonetheless, I feel strongly about it, so I will make it. Before looking at potential public health applications of genomic and genetic findings, I wish to note that the disease (risk) is regulated by genetic/genomic agents, by the environment, and, PERHAPS MOST IMPORTANTLY, by interactions between the genetic/genomic components and the environment (say, D= G + E + G*E). It seems logical that in many physiological disorders, G*E may be the largest determinant of D, and yet, we are all guilty of over-emphasizing the G part as if that alone will give all fixes. I think most people agree by now that, in the above equation, G by itself contributes very little to common and complex human diseases, and arguably, the biggest contribution involves G*E which makes meaningful studies of the E mandatory. But because we see a way of doing genomics (shall we say, sexy), and PERHAPS MORE IMPORTANTLY, we can not figure out quickly and cheaply WHAT type of environment is important for a given disease, we simply are guilty of abandoning the whole pursuit of the E. I am not saying that one should go after the E for its own sake, but without the E, we have no clue about G*E. Here are my related thoughts:

Until we get a good handle on at least the primary components of potentially relevant environmental components, and how to measure/observe them cost-effectively, we are less likely to make major advances in gene finding (I know the notice below does not want to hear about gene finding, but please read on); gene finding itself depends on how well we are able to handle the interactions;

Unless and until we make best efforts in (1) above, and thusly achieve some breakthroughs in gene finding, I doubt that major advances are possible in the public health domain for “genetic diseases”. How can one apply the poorly understood genetic information for public health advantage? Screen for candidates like AGT whose involvement is controversially very small? What if we find that the same M235T allele interacts profoundly with a certain environment, with much greater effect on D than any thing known before?

So, my bottomline recommendation is that, at least in some of the NHLBI epidemiological family studies, aggressively pursue developing and implementing "E" protocols and see if that would improve the impact of any known genetic variants or find new genes in subpopulations.

See response #6.

Have a concerted effort to reconsent individuals in key trials, obtain blood samples from them, and also get DNA from their family members.

In my view, the pooling of data from multiple studies, such as ARIC and CHS might be particularly useful when examining associations with of genetic variants with sudden cardiac death across a broader age range. This also would enhance the power of these efforts.

This question is hard to answer, especially because it invites everyone with a current vested interest in the samples to describe their next hoped-for grant. I believe you should support some kind of systematic search through candidate genes, using all known SNPs, to evaluate exactly what the impact of genes on relevant diseases is. No more mapping is needed. But very large properly done mouse experiments might be (but not the kind that are being done already).

I would also suggest:

Doing the above on data that already exist (no more big data collections are needed) in which the major putative environmental risk factors have been measured, to take them adequately and seriously into account in genetic studies, which is rarely done.

1. Establishing an "epistemological" task force to ask why our current methods fail so badly to generate reliable predictions (genetic or environmental, really). I say "epistemological" rather than "methodological" because the issues are deep and conceptual, not matters of more computing power, larger studies (despite the common wisdom that that is the way to go), and not matters of improved regression techniques. There are much more profound issues that need looking at.

RESPONSE 8: PUBLIC/CLINICIANS

Please recommend priorities and approaches for whether and how NHLBI might improve the understanding and utilization of genetic information by the general public (including specific population subgroups as necessary) and by practicing clinicians.

Unfortunately, much of the general public perceives cloning and stem cell research as the primary activities of geneticists. They also experience "genohype" in the media, falsely raising the expectations that the human genome project will cure many diseases in a short time frame.

Education about the realities of the potential of genomics to improve public health is urgently needed on many levels, ranging from elementary schools to health professionals. In addition to teaching the basics of human genetics and molecular biology, the notion of genetic determinism needs to be discredited. Similarly, the concept of "nature vs. nurture" need to be dispelled since disease susceptibility is very complex, involving genes, environment, access to health care, social conditions and a variety of other factors. Health education and behavior professionals need to be encouraged to undertake such activities in collaboration with geneticists.

If members of the public are to be asked to participate in research involving genotyping it is important that they understand the implications (confidentiality, privacy etc). In many population based studies of genotype distribution providing individuals with their genotype data is not advisable. This is generally not useful at individual level because the increased risk of having a particular genotype is not clear, and may be quite low.

It is necessary to have a much clearer understanding of functional genomics before this general approach is altered.

NHLBI should establish about 20 centers nation-wide to train and educate health care professionals at all levels, from medical students to older practicing physicians.

1. A concept is that although these centers will be distributed nationwide, it will function as a single organization with full data exchange capability and highly interactive scientific and administrative environment.

2. These centers will be funded by NHLBI in a competitive basis through a contract.

3. These centers will be typically located within Medical Schools, the primary entity of medical education in this country.

4. One center, in each location, will be manned by one principle investigator and a cohesive group of support staff: typically consisting of research nurses, technicians, and scientists and physicians.
5. One center will have at least one conference room with the state of the art audiovisual equipment, a clinic consisting of 1-2 rooms, a physician office, a phlebotomy room, a processing and storage room with centrifuge machine and -80C freezers, and a small laboratory. Extracted genomic DNAs can be sent to a central facility in one location to be stored (centralization) in order for additional future analysis to be easier). The center will serve as a liaison with surgeons and pathologist to retrieve human tissue.

6. Using the conference room, lectures will be given to medical students, interns, residents, university physicians, practicing cardiologists and primary care physicians. Materials will be developed centrally under the supervision and direction of board of directors of the Center, which reports to NHLBI. These lectures can be given in the context of CME (Continued medical education). These educational activities can be linked to pre-existing NHLBI initiatives, such as evidence-based medicine efforts. The Center will give lectures to patients themselves.

7. Board of the directors will determine about 10 most important diseases (such as atherosclerosis, hypertension, etc) for the Center to focus.

8. Importantly, Principal Investigator of the Center will be a physician-scientist who has demonstrated a good truck record both in clinical and basic research.

9. There will be frequent meetings with PIs to brain-storm and re-shape the direction of ongoing research.

10. The PIs may have their own gene(s) of interests which they have very substantial amount of knowledge and expertise. The PIs will generate hypothesis and make recommendations to the Board of directors.

11. The Center will serve as a window for tissue retrieval from patients who are undergoing surgery/autopsy.

NB:

Web-based approach to educate public is limited. Because people who are not motivated would never check into the web site. One-on-one (Scientist-on-primary care physician; primary care physician-on-patients) is the most effective way of knowledge transmission.

Centralization of the storage of samples and the generation of educational materials will save costs.

The Center will revitalize the dying academic medicine in medical school through funding. The Center will attract young medical students into academia.

The center will serve as a cohesive learning place where one can learn both the art of science and the knowledge of science.

FH actually would be a prime target for this. In the US, there are currently more FH patients than persons infected with HIV. It is a public heatlh priority. More funding for diagnosis, education and treatment of FH is the most obvious application of mature genetic understanding to the public health arena. The Netherlands has instituted an aggressive and sophisticated approach that could be a model for the US.

I have insufficient data to recommend priorities. But I will recommend a framework for the setting of priorities. NHLBI must examine its mandate, and the diseases covered within that mandate. Then the cost burden of each of the diseases must be established, both by and for morbidity and mortality. The relative merits of the utilization of genetic information for these diseases must be weighed and the benefits of this information in ameliorating morbidity and mortality assessed. Once this is done, NHLBI can determine which diseases, and which racial/ethnic subgroups to target with respect to getting the genetic message out.

Difficult problem. I am sure in many cases, despite the existence of a genetic mutation, there will be no change in mortality or morbidity. Thus, the genetic information will be considered irrelevant and will be ignored. How the genetic information is interpreted by the public is an important concern.

This is the last but perhaps the most important public health question. The field has "sold" its benefits to the public and politicians far beyond our ability to provide information which is useful to the average citizen. People believe that the genetic revolution, with the sequencing of the human genome, will fix illnesses and characteristics that bother them. Many practicing clinicians believe that therapeutic discovery is just around the corner.

NHLBI and the NIH have a unique opportunity to better educate the population about the realities of genetics research and its strengths and weaknesses. This is not be easy. Headlines about discovery lead to enhanced expectations daily. Many NIH supported scientists have become part of this hype. A long-term thoughtful educational program for the population and their elected representatives would serve the field much better and result in long-term commitment and support rather than the expectation and hope for instant benefits. Such research and application is not existing but necessary to realistically use the genetics revolution.

There is a huge need for better physician education in genetics of cardiovascular disease—this basically is not taught in our current training programs—the NHLBI could take a leadership position here by offering funding for special cardiovascular disease genetic fellowships.

We are currently piloting an approach, with request for MCHB HRSA funding, to do outreach education about hemoglobinopathy newborn screening. Would be happy to discuss with NHLBI.

Current IRB requirements are extremely taxing to investigators and the complexities and time required for IRB approval discourages young and even established investigators from entering science.

I am no expert here though biotech hype has not helped.

Research to address this question is urgently needed.

I believe that the NHLBI needs to approach this area with a "knowledge cannot hurt, and can eventually help" attitude, to educate physicians to encourage patients to participate in genetic information studies. This is not easy; e.g., a knowledge that one is in a high-risk stratum for breast or ovarian CA, while frightening, still persuades most patients to get frequent examinations. The NHLBI, in terms of heart disease, should be the bellwether for this type of education.

Train PHYSICIANS (especially primary care providers) about genetics and role of genetic variability in disease.

a. Target middle and high school age children for learning genetic language and concepts. They will teach their parents. Have genetics for non-science majors courses at the university level.

b. Partner with the American Heart Association to get one or two key messages across to the public.

c. Do not tell patients all of the details, only the key findings that might affect their clinical outcome. The danger is that the primary message may be lost in the details when large scale genetic screening of many genes is contemplated. Focus on patterns once they are elucidated. Consider how to do this with an unusual combination of individuals at the table-bioethicists, educators, and physicians.

In my view, NHLBI needs to clarify what is known and not known, and it can provide the public with a more reasonable set of descriptions of the challenges of moving forward, so the expectations of the public are based upon an unbiased view of the state of the art and prospects/promise of this work for the future.

I think the hype about the harm genetic testing can do to an individual (privacy, insurance etc) is way overemphasized, in fact for most genes the clinical effect (if any) of knowing genotype is very small. We need to emphasize the minimal risk and the benefits to society of such research.

Education is the key, but given the woeful lack of scientific literacy, education must start very early. An additional problem is the likely disparity among different segments of the general population. I'd focus on high school and college students by improving their science education, but this probably isn't the a role or a priority of NHLBI. NSF and other federal funding might be tapped.

The NHLBI could raise awareness of the diseases in high-risk groups through public education using resources such as publicity leaflets in supermarkets, shopping malls, and schools, and broadcasts on radio and television. It helps if a high profile celebrity figure with the disease could help in the campaign. In certain communities, inherited diseases are still considered a social stigma.

Again, even most geneticists can't keep up to date. Asking physicians to do it is a challenge, and in terms of public education really daunting. The best investment, perhaps, is in early education (K–12), but I think there is little reason to expect much yield. We'd have to start with teacher training.

It all sounds good, but the most important things, though more restricted and less glamorous, are (1) to get general health information (that is safe and secure, such as simply eating a balanced diet and not smoking, etc.) to the public; (2) strongly directive help to those truly at high risk, and (3) some form of better physician CME regimen; the latter is a real challenge; perhaps software that gives physicians believable advice (and is not manipulated by pharma or other supplier industries) would be the best use of resources.

But what do you tell physicians to do about the latest risk genotype for this or that trait, when the reality is that this is not really education so much as prescription to them for how to practice litigiously safe medicine? The problem is that we really don't understand risk nor how to translate retrospective risk to prospective risk—if such a translation is even possible.

RESPONSE 9: OTHER

Other information not specifically addressed by the comments above, but considered important and relevant to the use of genetic information in heart, lung, blood, and sleep public health efforts, would also be of considerable interest and value.

Genetic studies in isolation are only useful when the phenotype is obvious and usually rare—i.e., inherited in a dominant or recessive pattern. Most diseases require more sophisticated analyses of the effects of gene mutations on function. This will not occur until NHLBI provides funding to programs where geneticists/molecular biologists collaborate with scientists who study function at the protein, cell or organ (whole animal) level. The PPGs that I am familiar with at my academic institution may be strong in one or the other arena but to my knowledge are never strong in both.

My second recommendation is that academic centers need a financial incentive to develop diagnostics and therapeutics that are gene-based. Until this happens the importance of traditional medicine, i.e. the very non-scientific approach of cardiac catheterization and balloons/stents, will dominate due to the hospital's reliance on this clinical revenue. An evolution of the way cardiovascular medicine is practiced in the next 5–10 years requires that we train cardiology fellows now in the field of molecular medicine, and make "genetic medicine" profitable and rewarding for hospitals (as well as patients and cardiologists).

There has been great progress in gene array methods. Eventually, large-scale assessment of proteins will also be possible. However, there are limitations on the use of this information in genetics. Specifically, treatment of a number reflecting the abundance of an mRNA or a protein as a phenotype carries a heavy multiple testing penalty when applied on a large scale. It is highly fruitful to address this issue because the cost of covering as broad a sweep of biology using physiological phenotypes is prohibitive. In fact, genetic studies in humans have failed in part because they cover phenotypes chosen on the basis of feasibility.

My lab has identified genes whose expression is altered in obesity and diabetes. We have also identified loci that link with diabetes. We demonstrated that the genomics and genetics can be combined without losing the power to detect genetic linkage (not yet published). The approach is to reduce the dimension of the problem with either clustering or by computing principal components. The clusters or principal components are new traits that can be subject to a genome scan.

I believe this approach can be used on existing populations under study in many NHLBI projects. With the clustering approach, the clusters can be "seeded" with relevant physiological phenotypes. With the principal components approach, there is no bias and the PC's that emerge can be unexpected.

NHBLI has remarkable sources available for facilitating advances in public health genetics. Although informed consent issues are complex and need to be thoughtfully addressed, the extensive data and biological samples available from population-based studies could be especially useful for understanding the disease burden attributable to specific mutations. That is, the frequency of known disease susceptibility alleles vary in different population groups, and yet are often not well documented. Further, different cultural, environmental, behavioral, and social factors must influence penetrance of these disease susceptibility alleles. The combination of allele frequency and penetrance data, much of which could be derived from existing NHBLI data, would assist in quantifying the disease burden attributable to genetic factors in different population groups, and could lead to insights about new prevention strategies. Because many heart, lung, blood, and sleep disorders are likely to be multigenic, the use of large samples sizes will be needed to meet this goal.

We are currently developing research approaches to understanding the role of common polymorphisms in the social gradient in CVD. Two aspects of this are:

How, if at all, do common SNPs contribute to the inverse social gradient in CVD? What is the role of gene-gene, and gene-environment interaction?

1. What, if any, is the role of genetic variation in social mobility as an explanation i.e. "health selection" of healthier individuals/families into higher social classes, and vice versa?

Such population-based research is important to address neo-eugenic arguments about genetics and social class, and to aid our understanding of the role of common SNPs in health and disease.

In small clinical trials, we and others have produced evidence suggesting that central sympathetic inhibition by an a2-adrenergic agonist (clonidine) can significantly benefit heart failure and the post-MI patients. I feel there is a need for a large controlled outcome study with this therapeutic approach. (The poorly designed moxonidine trial in heart failure initiated by the drug's manufacturer is erroneously interpreted as having refuted the conceptual validity of this approach).

One of the greatest challenges facing us genetic epidemiologists is getting the message out about the difference between a simple Mendelian disorder, such a cystic fibrosis, and a complex multifactorial disease, such as hypertension. I don't think we have done a good enough job of educating the public or public health officials about this difference. For a simple Mendelian disorder, two flawed versions of an allele at a single location in the human genome guarantee the disease. For a complex multifactorial disease, two flawed versions of an allele at a single location increase the risk of disease. It is the comparison of the deterministic with the stochastic that we are not getting across. Complimenting this the paradox that the treatment of simple Mendelian disorders can require a substantial array of drug and physical treatments, as in the case of cystic fibrosis, yet successful treatment of the majority of cases of hypertension, a complex multifactorial disease, might be the DASH-Sodium diet with an active lifestyle. It bears pointing out that the rapid weight gain of lean muscle mass is a necessity of modern animal husbandry that has been successfully achieved for a trait that is in all likelihood complex, that is, polygenic, without the advantage of knowing the number or location of the genes involved. Yes, this result has been achieved by selective breeding. But for a human population, the genetic assimilation of a desirable genetic trait, such as leanness, could be alternatively obtained by alternative form of environmental modification: educational intervention through positive reinforcement. I leave the question of "When does a meme become a gene (or genes)?" open for you the reader to ponder.

I believe there is an opportunity to develop Centers of Excellence that would address the broad aspects of the genetic revolution from the bench to the bedside to the public arena. Such Centers of Excellence could play a pivotal role in advancing the field.

Clinical trials and population studies consume a disproportionate amount of research money. Yet scientists participation in them is nearly superfluous. The studies are run by, nurses, statisticians and administrators following protocols. It is important to invest far more effort, money and brains to generate the basic information necessary to reach truly evidence-based predictions. Prior designing large expensive trials sufficient information bridging the kinetic gap should be available. It is painful to see well designed basic and relevant mechanistic questions (even on the most devastating and common human diseases) in ~$250K research proposals go unfunded while many funded multimillion trials and population studies (sometimes on trivial and/or flowed premises) consistently fail to generate or suggests novel approaches to serious problems.

Please do not overlook the use of genetic/genomic information in disease when coupled with proteomic and other technologies to identify a critical subset of disease-relevant targets that are not just induced or overexpressed in the disease/tissue but are actually accessible and targetible for therapy in vivo—most targets coming from genomic screens will be very difficult to target specifically so that complications easily arise in clinical treatments—improvements are needed to use new techniques to delivery drugs and gene therapies to specific tissues in specific disease states for more optimal efficacious therapies. This point is almost always ignored in part because

it is not a critical barrier in most early screening approaches which are done in vitro in model systems outside the animal but then ultimately contributes to disappointing failure at the clinical trial stage. Many therapies that have failed clinically to date could be revived if they could be delivered swiftly and specifically to the desired site of action. That may indeed be attainable using new technologies today.

Partner with the FDA in requiring that all patients enrolled in drug trials have blood for DNA obtained so genes associated with arrhythmias (for example) can be identified (even if at a later date). It is critical that NHLBI and the FDA partner in this so that companies will not have an excuse for not having key patient populations tested—it may help industry by understanding how the drug is safe for all but a small percent of the population with certain genetic characteristics.

a. NHLBI could do a man power survey to find out exactly how much it costs to have the infrastructure to consent and obtain DNA samples from an average of 10 patients per day for genetic database generation. The cost now varies dramatically between institutions and most likely reflects naiveté on the part of the investigator on how much it actually takes for key infrastructure costs for this type of research. Gathering a team to determine the average realistic cost, especially considering consenting and obtaining samples over at least 2 shifts of the day, including vacation time, sample storage/transfer, equipment needed in clinic processing (e.g. refrigerated centrifuge, # freezers, liquid nitrogen), shipping to a remote location, bar coding, etc, will go far in helping investigators plan, should standardize the cost, and creating efficiencies. Of course this would not include cost of clinical endpoint measurements, laboratory isolation of DNA and testing, creation of cell lines, or statistical analysis, but would give a common ground for budgeting for the establishment of key database resources that combine clinical and genetic data.

b. We cannot emphasize enough the need to standardize definitions of clinical endpoints and tests such as CK-MB, troponins, etc and the timing.

Consent forms need to be appropriately broad to allow unthought of hypotheses to be tested using data collected form clinical studies.

Maybe the hard truth is that people will be hedonistic wherever possible, that we're wonderfully privileged in terms of an easy lifestyle with ad libitum nutrition. That is what people like and they seem unwilling to give it up for presumed health reasons.

More seriously, I am just completing my role in the large Mdecode project and I think that experience has been very instructive. But what it instructs is not more and bigger research, but more and more careful thought about the problem itself. I believe the issue is epistemological.

Despite ever accelerating investment, few issues seem near to closure (this is not just so for heart disease, but for most chronic diseases).

One need is to focus the minds of investigators by imposing some form of accountability, and prioritizing current practice, with real closure rules for things that aren't going anywhere even after many years of investment. The current peer review and administrative systems are unable to dislodge vested interests that are long in the tooth.

Let's see if we can do something real for the risk factors that we actually do understand, or the genes that really are causing disease (like LDLR, for example), rather than endlessly fishing for new (usually very minor and ephemeral) candidate genes, which is what ever more mapping and association studies do.

The problem above all is that neither in genetics nor in environmental epidemiology do we have the causal phenomena understood so that we can develop reliable, replicable estimates of risk or predictions. This is not due to insufficient statistics, computers, molecular technology, or sample size. It won't be solved by 300,000 markers, array readers, international genetic meta-analytic consortia, or huge longitudinal clinical trials, and we already know of many of the reasons why. It is not because somehow previous Study Sections approved poorly designed studies or the right regression or genetic epidemiological methods were not available.

The likely explanation for the general failure of current approaches is that our causal notions and inferential framework—the questions we ask and the methods we apply—are not appropriate for the problem. Or, perhaps, that the objective of preventing disease by identifying risk factors in the way we conceive of it simply won't work for risk factors of small effect. To do this, we need to think of redirecting and reconfiguring research, but in fundamental rather than superficial ways.

This is not popular to say, but doesn't change the reality. I think there is a need for a high priority 'task force' to try to understand address the real underlying problem that, I believe, is epistemological. Of course, one cannot order up creative rethinking with an RFA, nor can they be settled by minor changes in priorities, nor by a few senior insiders with vested interests who are too dependent on the current system, or people too old to think afresh. It should be a serious effort disengaged from any specific bureaucratic turf within the Institute.

It may be possible to sow seeds to increase the odds that really new ideas will grow.